

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-937/20-975/20-976/S-003**

**Medical Review(s)**

**DIVISION OF MEDICAL IMAGING AND  
RADIOPHARMACEUTICAL DRUG PRODUCTS**

Medical Officer Review

NDA#                20-937, 20-975, 20-976  
Supplement #     1

M.O. Review #    1

Date of letter: 3/29/2002  
Date FDA received: 4/1/02  
Date reviewer received: 4/23/02  
Date review completed: 11/22/02

Drug name:                      Gadolinium-DTPA/Bismethoxyethylamide Injection  
Generic name:                  Gadoversetamide  
Proposed trade name:        Optimark™ Injection  
Chemical name                 Gadolinium-DTPA/Bismethoxyethylamide (gadoversetamide)

Sponsor: Malinkrodt , Inc.  
              St. Louis, MO 63042

Pharmacologic Category:     MRI Contrast Agent

Indication(s):                 CNS: " ... in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues "  
Liver: " ... in the liver patients who are highly suspect for liver structural abnormalities on computed tomography."

Dosage Form(s) and  
Route(s) of Administration,  
Directions for Use:             0.2 mL/kg (0.1 mmol/kg) in solution by an IV bolus and at a rate of 1-2 mL/sec

<b>SUBMISSION/TYPE</b>	<b>SUBMISSION DATE</b>	<b>CDER DATE</b>	<b>ASSIGNED DATE</b>	<b>CONTENT</b>
Amendment (BZ, SU)	13-Jan-03	13-Jan-03	13-Jan-03	Safety Update

NDA Drug Classification:

Related Drugs: Omniscan-gadodiamide, ProHance-gadoteridol, Magnevist-Gadodimeglumine

Related Reviews: Pharmacology/Toxicology Review dated: December 13, 2002

**Table of Contents**

1. General Information	1
2. Table of Contents	2
3. Executive Summary	2
4. Introduction and Background	5
5. Significance Findings from Chemistry, Animal Pharmacology and Toxicology, and /or Microbiology	5
6. Pharmacokinetics	6
7. Pharmacodynamics	8
8. Important information from Related INDs and NDAs	8
9. Sources of Clinical Data	9
10 Overview of Clinical Trial	11
10. Safety variables and Safety Assessments	12
10. Integrated Review of Safety	16
11. Conclusions	29
12. Recommendations	29
13. References	30

Executive Summary

1. RECOMMENDATIONS

1.1. Recommendations on Approvability

Optimark may be used with the power injector at rate 2 ml/sec, the rate for which it is currently approved. The study found minor differences in expected directions between saline and Optimark as well as among OptiMARK injections administered at increasing rates, however, the study was not designed, executed and analyzed well enough to detect true differences, if present.

1.2. Recommendations on Phase 4 Studies and Recommendations on Postmarketing Studies and/or Risk Management Steps

If the sponsor intends to pursue administration of OptiMARK by power injector, the study

should involve much greater number of patients, but not healthy subjects, and the trial should be executed in such a way that all critical data are obtained. The data should then be analyzed by a generally accepted methodology in order to obtain reliable, non-ambiguous results.

## 2. SUMMARY OF CLINICAL FINDINGS

### 2.1. Brief Overview of Clinical Program

This Phase 4, single center, randomized, blinded study was intended to compare the safety of OptiMARK administered via power injector at three dose rates, a placebo administered at the same rates, and OptiMARK administered via hand injection. Normal, mostly young, normal volunteers were randomized to receive a single intravenous administration of (0.1 mmol/kg) OptiMARK or normal saline (0.2 ml/kg) by power injector at rates of 2, 4, or 6 ml/sec, or 0.2 mL/kg OptiMARK by hand injection at a rate of approximately 2 ml/sec. The currently approved dose is 0.2 mL/kg (0.1 mmol/kg) in solution by an IV bolus and at a rate of 1-2 mL/sec. No imaging, or efficacy evaluations were performed.

Each subject underwent a physical examination at screening (within 24 hours prior to dosing) and 24 hours after dosing. Vital signs (diastolic blood pressure, systolic blood pressure, pulse, respiratory rate and temperature) were performed at screening (within 24 hours prior to dosing), 15 minutes prior to dosing and immediately, 30 minutes, 1, 2, 4, and 24 hours post dosing. Additionally, an automated system was used to monitor blood pressure and pulse rate beginning 15 minutes prior to dosing and continuing for 30 minutes after the start of the injection. Measurements were collected 15 minutes prior to dosing, immediately prior to the start of the injection, and 1, 3, 5, 10, 15, 20, 25, and 30 minutes following the start of the injection. Subjects underwent screening laboratory tests (Hgb, Met, ALT and AST) according to the study site's established procedures. The Principal Investigator assessed clinical significance of abnormal values and, if necessary, discontinued subject participation. Standard laboratory evaluations (chemistry, hematology, and urinalysis) were performed 2 hours prior to dosing and 2 and 24 hours after dosing. In addition, intermittent 12-lead electrocardiogram (ECG) monitoring was obtained 15 minutes prior to dosing and continued for 30 minutes after study drug administration. Rhythm strips were obtained 15 minutes prior to dosing, immediately prior to the start of the injection and 1, 3, 5, 10, 15, 20, 25, and 30 minutes following the start of the injection. Additional ECG recordings were collected at screening (within 24 hours prior to dosing) and 1, 2, 4, and 24 hours post injection.

A total of 144 healthy normal volunteers were enrolled, with 140 dosed, at a single study site. The health status of the volunteers was based on an assessment of medical history, physical examination, laboratory values, and cardiovascular function during a screening evaluation by a medically-certified individual at the site.

### 2.2. Efficacy

N/A

### 2.3. Safety

The question of relatively high proportion of patients exhibiting QTc prolongation, as listed in the current labeling, was not addressed appropriately in this amendment although the QTc prolongation was measured, analyzed and commented upon in the safety section. There is a need to investigate QTc data from a patient population not necessarily healthy volunteers. Collection and analysis of QTc data in this submission was not conducive to rendering an informed assessment. The sponsor stated in the introductory letter that this issue would be addressed separately as a Phase 4 commitment and such a trial has apparently has been completed. The association of the use of OptiMARK with hypotension found in the original NDA review was confirmed by this study and acknowledged by the applicant. An association with sinus arrhythmia was found anew and acknowledged by the applicant as well. The results also suggest an apparent association of OptiMARK administration with impaired liver function and an alteration of several hematology parameters, but the results are inconclusive since the abnormalities were not followed up until resolution. Trends for increased number of adverse events with the drug as opposed to saline, and increased safety risks mentioned above with OptiMARK administered via power injector as opposed to the drug administration by hand were observed, but the results are inconclusive because of inappropriate data collection and analysis, small number of normal subjects enrolled per group and absence of patients in the sample. Likewise, the dose response (rate response) relationship could not be evaluated with any degree of certainty.

### 2.4. Dosing, Regimen and Administration

OptiMARK (0.2 mL/kg) or saline (0.2 ml/kg) were administered as a single intravenous injection by power injector at rates of 2, 4, or 6 mL/sec, or 0.2 mL/kg OptiMARK by hand injection at a rate of approximately 2 mL/sec.

### 2.5. Drug-Drug Interactions

The drug was administered to normal volunteers who scarcely used other medications. No interaction was observed in 4 women on steroid contraceptives.

### 2.6. Special Populations

N/A

Note: All details of special concern within a particular context of specific safety aspects of OptiMARK studied in this submission (besides subtitles) are in **bold letters**.

## Clinical Review

### **1. INTRODUCTION AND BACKGROUND**

Magnetic resonance imaging (MRI) of the brain began with the use in diagnosing neoplastic conditions. Gd/DTPA was approved in the low dose (0.1 mmol/kg) in 1988 for intracranial neoplastic lesions.

#### 1.1 Material Reviewed

Clinical data appears in volumes 1.1 – 1.8 and were reviewed in full.

### **2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY**

#### 2.1. Chemistry/Manufacturing Controls

Please refer to initial Chemistry review for NDA 20-937.

#### 2.2. Animal Pharmacology/Toxicology

Please refer also to initial Pharmacology/ Toxicology Review in NDA # 20-937, Archival Copy and the Pharmacology/Toxicology review of this submission dated December 13, 2002 by David Bailey, Ph.D.

### **3. PHARMACOKINETICS AND PHARMACODYNAMICS**

#### **3.1 Pharmacokinetics**

No new issues as this submission studied the approved dose. Please refer to initial Biopharm review for NDA 20-937.

#### **3.2 Pharmacodynamics**

##### **3.2.1 Relevant Human Experience**

Since first approved in 1988, the clinical applications of the gadolinium containing contrast agents expanded from diagnosing neoplastic conditions to non-neoplastic diseases. Currently it has been used in diagnosing infection, vascular disorders, trauma and diseases of the white matter of the brain as well as liver lesions.

Among patients with compromised immune system, the most common use is in the diagnosis of toxoplasmosis where lesions are detected in the basal ganglia and gray-white matter interphase in cerebral hemispheres. In patients with HIV, the contrast enhanced MRI is used for detection of meningeal pathology. Likewise, the diagnosis of viral encephalitis due to Herpes simplex virus type 1 can be helped by contrast MRI. In addition, lesions can be seen with brain abscess, in both the cerebritis as well as capsule stages of abscess formation in the brain. This is due to the blood-brain barrier disruption. In case of meningeal disease, as demonstrated by contrast MRI, the presentation is not specific for infection, but may appear the same with surgery, trauma or neoplastic disease.

Three patterns of enhancement can be seen in cerebral infarction. These are intravascular enhancement, vessel enhancement and meningeal enhancement. Lacunar infarcts can be seen easier by MRI than by CT. Cerebellar infarcts can also be identified.

Diseases of white matter can also be diagnosed as lesions are identified in multiple sclerosis as well as other conditions such as acute disseminated encephalomyelitis. The response of MS lesions to short courses of high-dose intravenous methyl- prednisone correlating with clinical improvement have been observed by the MRI. Parenchymal contrast enhancement because of alteration of the BBB can be observed several days after trauma.

### **3.2.2 Important Information from related INDs and NDAs**

Three other gadolinium containing chelates are currently approved. Gadodiamide (Omniscan) only for the low dose, gadodimeglumine (Magnevist) for the high dose and Gadoteridol (ProHance) for the low (0.1 mmol/kg) and high dose (0.3 mmol/kg). Although efficacy with all the three agents is roughly the same with the low dose, the higher is described as advantageous in some lesions.

All the four approved Gd compounds have different structures and different properties, mainly, osmolality, viscosity, stability of the chelate in vitro and likely also in vivo. Gadodiamide and Gd/DTPA dimeglumine have linear structure, while gadoteridol has a circular structure. The structure determines the properties of the agent. Gd/DTPA dimeglumine is considered a high osmolar agent, while the other two have low osmolality. Optimark may be considered to have an intermediate osmolality. The thermodynamic binding constant ( $\log K_{eq}$ ) is 22.1 for Magnevist, but 23.8 and 16.9 for ProHance and Omniscan, respectively. Viscosity is 2.9 CP for Magnevist, but 2.0 CP, 1.4 CP and 1.3 CP for Optimark, Omniscan and ProHance, respectively. In vitro stability as measured by dissociation in 0.1 M HCl is  $20 \times 10^{-3}$ ,  $6.3 \times 10^{-3}$  and  $1.2 \times 10^{-3}$  for

Omniscan, ProHance and Magnevist, respectively. However, this does not reflect the in vivo stability. The latter may be judged, among other means, by transmetallation of the chelates in vivo as seen from abnormal elimination of ions other than Gd in urine. Some of these parameters are not yet available for Optimark since it is relatively a new agent.

#### 4. DESCRIPTION OF CLINICAL DATA AND SOURCES

##### 4.1 Sources of Clinical Data

This Phase 4, single center, randomized, blinded study was intended to compare the safety of OptiMARK administered via power injector at three dose rates, a placebo administered at the same rates, and OptiMARK administered via hand injection. Mostly young, normal volunteers were randomized to receive a single intravenous administration of 0.1 mmol/kg OptiMARK or normal saline (0.2 ml/kg) by power injector at rates of 2, 4, or 6 ml/sec, or 0.1 mmol/kg OptiMARK by hand injection at a rate of approximately 2 ml/sec. No imaging or efficacy evaluations were performed..

After subject eligibility was assessed, written informed consent was obtained from each participant. The subject's medical and surgical history, including medications taken within 24 hours prior to the study procedure, were recorded. Medically certified personnel performed a physical examination. Safety was assessed by, vital signs (blood pressure, pulse rate, temperature, and respiratory rate), ECG, clinical laboratory evaluations, and adverse events (AEs).

##### Inclusion Criteria

1. Men or women 18 years of age or older.
2. If women of reproductive potential (not surgically sterilized and/or not post menopausal), the subject practiced adequate non-hormonal contraception for at least 3 months prior to, and for the duration of study participation and had a negative urine pregnancy test at the screening evaluation.
3. **Weighed within 15% of the ideal weight for height and frame**
4. Subjects were in good health and physical condition as determined by medical history, complete physical examination, clinical laboratory evaluations, and electrocardiogram as assessed during the screening evaluation.
5. Subjects had the ability to understand the requirements of the study, provided written consent to participate, and agreed to abide by the study requirements.
6. Subjects underwent screening laboratory tests (Hgb, Hct, ALT and AST) according to the study site's established procedures. **The Principal Investigator assessed the clinical significance of abnormal values and, if necessary, discontinued subject participation.**

##### Exclusion Criteria

1. Subject had previously entered this study, or had participated in a previous study involving OptiMARK.
2. Subject had received any investigational drug within 30 days of admission into this study.
3. Subject had a medical condition, serious intercurrent illness, or extenuating circumstance that would significantly decrease study compliance, including all prescribed follow-up.
4. Subject with known or **suspected** hypersensitivity to a gadolinium-based contrast agent.
5. Subject was pregnant or lactating.
6. **Subject had a dispersion in QT readings greater than 60 msec on the screening ECG.**
7. Subject had undergone an invasive procedure within 30 days prior to enrollment in the study.
8. Subject received an iodinated contrast agent within 72 hours prior to study drug administration.

#### **Removal of Subjects from Therapy or Assessment**

It is not stated in the submission how many subjects were actually selected for the study and dropped because of the reasons listed below in this section. Likewise, it has not been mentioned, for example, how many were excluded because “the QT dispersion was greater than 60 msec”.

Subjects were free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. A subject’s participation in the study could have been discontinued at any time at the discretion of the Investigator. The subject who was dosed but then voluntarily withdrew was not replaced. The following were considered justifiable reasons for the Investigator to remove a subject from the study:

- A subject was uncooperative (included failure to appear at one or more study visits).
- A subject was erroneously included in the study.
- A subject developed an exclusion criterion or concurrent disease.
- A subject suffered an AR that, regardless of seriousness, prohibited further participation in the study.
- A subject suffered an AE that, in the judgement of the Investigator or Sponsor, presented an unacceptable consequence or risk to the subject.
- The Sponsor terminated the study.
- The subject or the subject’s legal guardian refused clinical trial material administration.

If a subject decided to discontinue participation in the study, he or she was to be contacted, if possible, to obtain information about the reason(s) for discontinuation and any AEs. Whenever possible, the subject was to return to the clinic for the 24-hour clinical assessments. The Investigator provided a written report on the Subject Disposition page of the CRF describing the reason for discontinuation.

**If the Sponsor, Investigator, or FDA officials discovered conditions during the study that indicated that the study or participation by the clinical site should be terminated, this action would have taken place after appropriate consultation between the Sponsor and Investigator.** Conditions that would have warranted termination of the study included, but were not limited to, the following:

- **The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study**
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug

A study conducted at the study site also warranted termination under the following conditions:

- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent FDA regulations
- The submission of knowingly false information from the research facility to the Sponsor or FDA
- **Insufficient adherence to protocol requirements**

#### **4.2 Overview of Clinical Trial**

The aim of the trial under scrutiny here was to document safety of the approved dose (0.1 mmol/kg) of Gd/DTPA bismethoxyethylamide in normal young adults after administration by power injector.

As it will become apparent from the evaluation below, for example, by noncompliance of the sponsor with the details of the planned protocol design and analysis not only jeopardized the testing of the hypothesis for which the trial was designed, but the traditionally accepted measures of quality designs and experimentation, in general, cannot now be applied in the interpretation of the results, since the underlying assumptions were not met. As another example, a line listing was not provided of QTc changes, only CRFs, and, in many instances (such as vital signs) descriptive statistics were substituted for a case by case analysis.

With the above, as introduction, in mind, the trial and its design, which without such an introduction may seem adequate, can be now analyzed on its merit. The same holds for the results of the trial presented.

#### **Safety Variables and Safety Assessments**

The safety of OptiMARK was monitored using the following parameters: occurrence of AEs, vital signs, continuous ECG monitoring, physical examinations, clinical laboratory evaluations,

and prior and concurrent medication use. If clinically significant changes from baseline of any safety parameter were observed, these changes were documented on the Adverse Events page of the CRF. The Investigator continued to monitor the subject until the parameter returned to baseline or **until the Investigator determined that follow-up was no longer medically necessary. The Investigator used medical judgement in deciding whether or not to continue the subject's participation in the study.**

**The Sponsor defined clinical significance as any variation in a safety parameter that had medical relevance and resulted in an alteration of medical care.** The clinical significance of any changes in safety parameters (excluding AEs), as defined by the Sponsor or Investigator, was noted on the Subject Disposition page of the CRF.

#### **Adverse events**

Adverse events were monitored continuously from the time the subject signed the consent form until approximately 24 hours after administration of the dose.

#### **Physical exam**

A medically certified individual performed a physical examination at baseline and at the 24-hour follow-up assessment. Whenever possible, the same medically certified individual performed both physical examinations. The findings of each examination were recorded on the CRF. Each physical examination included the following physical observations: General Appearance; Skin; Head, Ears, Eyes, Neck, and Throat; Neck; Chest; Heart; Abdomen/Pelvis; Extremities; and Neurological.

#### **Vital Signs**

Vital signs, including blood pressures (mmHg), pulse rate (beats/minute), respiratory rate (breaths/minute) and body temperature were obtained and recorded before and after treatment. Systolic and diastolic blood pressures and pulse rates were measured at screening (within 24 hours prior to dosing), 15 minutes prior to dosing, immediately prior to the start of the injection (baseline), and 1, 3, 5, 10, 15, 20, 25, and 30 minutes, and 1, 2, 4, and 24 hours after injection. Respiratory rate and body temperature measurements were made at screening (within 24 hours prior to dosing), 15 minutes prior to dosing (baseline), immediately following ( $\pm 15$  min.), 30 minutes, 1, 2, 4, and 24 hours post study drug administration.

#### **Electrocardiograms**

Twelve-lead electrocardiograms (ECG's) were obtained at screening, 15 minutes prior to dosing, immediately prior to the start of the injection (baseline), and 1, 3, 5, 10, 15, 20, 25, and 30 minutes and 1, 2, 4, and 24 hours after injection. Assessment included duration of the PR interval, QRS complex, QT interval, and QTc interval (corrected according to Bazett's formula).

In addition, the ECGs were evaluated for heart rate, and changes in T-wave morphology and/or the occurrence of U-waves. The core facility's medically-certified cardiologist made such interpretations and provided the clinical significance without knowledge of the subject's treatment group.

Each ECG interval was measured using an automated analysis package. However, each QT interval was over read by the core facility's medically-certified cardiologist using electronic calipers. **Each value represented a mean of 3 cardiac cycles and three leads (II, V2 & V5).** These over-read values were used in the analysis of the data. In addition, PR interval and QRS complex durations not interpreted by the analysis package, because of poor signal quality, were also over read by the cardiologist. The core facility's medically-certified cardiologist interpreted each ECG within 24 hours of receipt. **Each interpretation assessed clinical significance.** The cardiologist possessed no knowledge of the subject's treatment group.

#### Clinical Laboratory Evaluations

Clinical laboratory evaluations, including hematology, clinical chemistry, and urinalysis assessments, were obtained at baseline, and at 2, and 24 hours after study drug administration.

A central laboratory was used \_\_\_\_\_

The following laboratory tests were performed:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, total white blood cell (WBC), count differential WBC count, including: lymphocytes, neutrophils, bands, monocytes, eosinophils and basophils
- Clinical Chemistry total bilirubin alkaline phosphatase (ALP), alanine aminotransferase (ALT), creatinine, uric acid, phosphorus, total serum albumin, cholesterol, potassium, iron, magnesium, direct bilirubin aspartate aminotransferase (AST) blood urea nitrogen (BUN) glucose, total protein, creatine phosphokinase (CPK) lactate dehydrogenase (LDH) sodium, copper, zinc
- Urinalysis
  - color
  - pH
  - glucose
  - bilirubin
  - specific gravity
  - protein
  - ketones
  - blood
- Serum Calcium Analysis

**In vitro tests have confirmed that in the presence of OptiMARK, a chemical interference in \_\_\_\_\_ assays of calcium can occur.** Therefore, all calcium values (regardless of the treatment) were determined utilizing \_\_\_\_\_ (p.1.153, par.2).

All laboratory tests with clinically significant changes **were repeated** following the procedure (as agreed upon by the Investigator and the medical monitor) until the value(s) returned to baseline **or until the Investigator and the medical monitor agreed that a further follow-up was no longer medically necessary for the subject.** Copies of any additional laboratory tests were included with the CRF.

#### **4.3 Post marketing experience**

Data in this submission are tenuous, and thus not considered a reasonable basis to warrant a dedicated discussion.

#### **4.4 Literature review**

N/A

### **5. CLINICAL REVIEW METHODS**

The subjects enrolled in this trial were young adults in their teens and twenties, thus, favoring healthier segment of the population. However, the inclusion criteria in the original protocol are even more equivocal for the purpose of the study, as already stated, and as it will be emphasized later (for example, “a subject’s participation in the study could have been discontinued at any time at the discretion of the Investigator”). For subject demographics, please, refer to the next section. Given the intent of the study to assess the utility of the procedure with the agent administered by power injection, the stringent inclusion and exclusion criteria limit the applicability of results obtained for clinical use of this agent in patients.

Thus, a rigorous in-house analysis of this safety data might not have been possible and did not appear warranted due to the inappropriate content (for example, only 20 normal volunteers per group) and format of the data (for example, three QTc interval prolongations averaged and only the mean analyzed) and analyses (for example, averaged QTc intervals evaluated by descriptive statistics) provided. Several tables which still appear somewhat relevant despite all the limitations of the data due to the design as well as conduct of the studies were transferred directly from the submission listed and will be commented upon as needed.

The aim of the trials under scrutiny here was to document safety of 0.1 mmol/kg of Gd/DTPA/Bismethoxyethylamide administered by a power injector in normal volunteers.

Each subject was randomized to one of the seven treatment groups listed in table below. Each received a single intravenous administration of the study drug or placebo, followed by a normal saline flush, at the volume and rate specified in the table according to the randomization schedule provided by the sponsor.

Treatment Group	Study Agent	Injection Rate	Normal Saline Flush	Injection Method
1	0.1 mmol/kg OptiMARK	2 ml/sec	5ml at 2 ml/sec	Power
2	0.1 mmol/kg OptiMARK	4 ml/sec	5 ml at 4 ml/sec	Power
3	0.1 mmol/kg OptiMARK	6 ml/sec	5 ml at 6 ml/sec	Power
4	Normal Saline	2 ml/sec	5 ml at 2 ml/sec	Power
5	Normal Saline	4 ml/sec	5 ml at 4 ml/sec	Power
6	Normal Saline	6 ml/sec	5 ml at 6 ml/sec	Power
7	0.1 mmol/kg OptiMARK	2 ml/sec	5 ml at 2 ml/sec	Hand

The volume of normal saline was equivalent to the volume of OptiMARK dose based on the subject's weight (0.2 ml/kg). The appropriate volume of contrast agent or normal saline was calculated on a weight basis. For subjects randomized to the three placebo (saline) groups, the dose was calculated and the equivalent volume of normal saline (0.2 mL/kg) was administered. Each subject enrolled in the drug arm of this trial received a single intravenous administration of OptiMARK.

## 6. INTEGRATED SUMMARY OF EFFICACY

Efficacy was not a subject of this submission.

### Efficacy Results, Tabulation of Individual Response Data and Efficacy Conclusions

Efficacy analyses were not performed for this study.

## 7. INTEGRATED REVIEW OF SAFETY

### Disposition of Subjects and Data

A total of 144 normal healthy, mostly young volunteers were enrolled and 140 were dosed in this study; 20 subjects in each treatment group. Four subjects enrolled, dropped prior to dosing, and were replaced.

In reference to timing of safety evaluations the sponsor states (p.1.160, par. 1, l.1): **“There were numerous minor timing violations in laboratory specimen collection and vital sign acquisition. These violations were determined not to adversely affect subject safety.”**

Also, the QT dispersion which was used as one of the exclusion criteria was defined by the sponsor as **“... the difference between the longest and shortest QT interval from a 12 lead ECG”** (p.1.160, par. 2, l.1). Although it might have been used as the exclusion criterion it was not subject of analysis (ibid.) and, therefore, it might have been used arbitrarily.

Clinically significant vital sign changes were defined as systolic blood pressure changes >20 mmHg, diastolic blood pressure changes >15 mm Hg, pulse rate changes >15 beats per minute, respiratory rate changes >10 breaths per minute, and temperature changes >1.5 degree (C).

**Demographics (n = 140)**

Age (years)		
	Mean + Standard Deviation	36.7 ± 17.4
	Range	18 to 79 years
Sex		
	Men	79 (56.4%)
	Women	61(43.6%)
Race		
	White	111 (79.3%)
	Black	22 (15.7%)
	Other	6 (4.3%)
	Asian	1 (0.7%)

The use of concomitant medications was comparable across treatment groups. The most commonly used medications were oral contraceptives (4 subjects, 2.9%) and hormone replacement therapy (2 subjects, 1.4%).

**Drug-Drug and Drug-Disease Interactions**

Drug-drug and drug-disease interactions were not examined for this study.

**By-Subject Displays**

By-subject displays were not constructed for this study.

**Goal of safety evaluation**

Free gadolinium may be expected to exert toxic effect clinically and on laboratory parameters since it is a heavy metal. Other heavy metals are well known for their general toxicity, most notably lead (Pb) upon accidental ingestion of a lead-containing paint by children.

**Current priorities in safety assessment**

As mentioned in the pre-clinical section, low levels of gadolinium interfere with calcium channels and related signalling. That may be related to the main tangible quantitative safety concern with OptiMARK, namely, a prolongation of QTc interval. The current labeling describes

some QTc prolongation in patients. Consequently, until this question is fully resolved, assessment of the QTc should be the focus of any safety evaluation. Although the sponsor states that a separate study will address this issue, it will likely not be done in the context of the use of the power injector. Therefore, the dilemma of cardiac assessment as approached in this submission will be addressed first.

#### **Extent of Exposure**

A total of 144 subjects were enrolled in the study. Four dropped prior to dosing. A total of 140 subjects were dosed in this study; 20 subjects in each treatment group. Four groups were administered 0.1 mmol/kg of OptiMARK, and 3 groups were administered saline. The injection rates for OptiMARK were 2 mL/sec administered by hand bolus injection and 2, 4, and 6 mL/sec administered by power injection. The mean volume administered for each OptiMARK treatment group was 14.5, 14.5, 13.9, and 13.4 mL respectively. The volume ranges for the OptiMARK groups were 10.6 to 18.8, 11.0 to 18.8, 11.4 to 16.6, and 10.4 to 17.4 mL, respectively. Saline was injected using a power injector at rates of 2, 4, and 6 mL/sec. The mean volume for each saline treatment group was 13.8, 13.9, and 14.7 mL, respectively. The volume ranges for the saline treatment group were 9.2 to 17.4, 10.4 to 18.2 and 11.0 to 19.8 mL, respectively.

#### **Selection of trial population**

The human population described in this submission were “... **primarily young healthy adults**” (p.1.194, par 2). It is further stated that: “... The cardiologist, in his blinded review of the ECGs, also described a **high incidence of sinus bradycardia and sinus arrhythmia** in the study population. For this subject population, primarily young healthy adults, the cardiologist indicated that these observations were within normal limits and not the result of treatment.”

QTc dispersion greater than 60 msec was one of the exclusion criteria. As mentioned earlier, the QT dispersion was defined by the sponsor as “... **the difference between the longest and shortest QT interval from a 12 lead ECG**” (p.1.160, par. 2, l.1). Although it might have been used as the exclusion criterion it was not subject of analysis (ibid.) and, therefore, it might have been used arbitrarily. The reason for use of QTc dispersion as an exclusion criterion is unknown, but any limitation to further narrow the healthy subject spectrum in the study was unfortunate as, strictly speaking, the conclusions now can apply only to such a limited population (young healthy adults with a negative QTc dispersion screen).

#### **Sponsor's evaluation of cardiac data**

In considering the cardiac results, it is worth repeating that each QT interval was over read by the core facility's medically-certified cardiologist using electronic calipers and each value used for analysis represented a **mean of 3 cardiac cycles and three leads (II, V2 & V5)**. These over-read and averaged values were deployed in the analysis of the QTc data.

Such an averaging of QT interval data is unacceptable since it destroys the purpose of QTc analysis. The latter is based on the detection of any single occurrence of a QTc prolongation of certain length, summing up the total number of subjects in whom it was observed and expressing the outcome as a percentage of total number of subjects (patients).

#### **Discrepancy between the current and earlier cardiac data**

In addition, referring still to the QTc evaluation, as noted earlier, the current package insert for Optimark describes association of the drug injection with a more than 30 msec prolongation of QTc in almost 20% patients (18/93). To investigate this effect sensibly and definitively, an adequate number of patients should have been enrolled. Instead, a dose-ranging power injector study was performed with only 20 normal subjects per a treatment group. Twelve measurements of QTc were performed per subject up to 24 hrs post-injection. In addition, The Sponsor did not analyze primary data appropriately. Instead of counting and recording each QTc abnormality as it occurred, three individual QTc measurements were averaged and only the mean was reported in the respective table. This practice is inappropriate and may be misleading. Such data can not be relied upon in the context of an ordinary discussion about potential clinical significance of reported QTc abnormalities. A required primary data for an in-house analysis of QTc information can not be retrieved from the current submission.

To further confound the data interpretation a saline control was included for each treatment group with the power injection, but not in the control group with hand injection.

As reported in this submission, the rate of QTc abnormalities in **healthy young adults** under these circumstances does not approach that seen in **patients** as described in the the original NDA submission (2-5% versus 20%). At the same time, when the power injector was used, the rate of QT abnormalities (cumulative QTc prolongation totals in three subgroups: 21-25 msec, 21-25 msec and 31-60 msec) in healthy adults appears somewhat higher with the drug (57 prolongations reported) than with saline (50 prolongations reported) as shown in Table 12.5.3-2, Vol.1, page 1.186). Furthermore, the rate seen with the drug injection by hand appears similar to that obtained with saline administered by the power injection. No associated changes of heart rhythm were reported.

#### **Absence of valid key results**

Other similar questions also abound. Would the results with OptiMARK, even if properly analyzed, obtained with the small number, 20 subjects per group, show the same percentage of QTc prolongations as with larger number, for example, 200 subjects? How would this compare with the data in the original NDA? Are 20 subjects a sufficient group size to assess the effect of the power injector and different drug doses in a healthy population? Is it permissible to evaluate

the effect of the power injector in normal subjects when the gadolinium contrast is intended to be used in patients?

**No basis for definite conclusions on cardiac safety**

No reasonably definite conclusions can be made from this study in regard to cardiac safety in the intended patient population. Even a preliminary informed conclusion can not be made regarding the safety of power injection in healthy young adults with QTc dispersion, and, for the reasons discussed in the previous five paragraphs, in young adults without QTc dispersion. Answers to all the questions in the previous paragraph may only be tentative. More so, as the original NDA review revealed a definite cardiac effect manifesting as a QTc prolongation and bradycardia.

**Adverse Events**

Table 1 below shows subjects with adverse events by treatment groups. All of the 64 adverse events were rated as mild or moderate.

Injector type	Hand	Power		Power		Power	
Treatment	OptiMARK	OptiMARK	Saline	OptiMARK	Saline	OptiMARK	Saline
Rate (ml/sec)	2	2		4		6	
Number	20	20	20	20	20	20	20
Total number	2(10)	5(25)	5(25)	9(45)	4(20)	10(50)	8(40)
Administration			3(15)		1(5)	2(10)	1(5)
Body as a whole	1(5)	2(10)	2(10)	3(15)	2(10)	4(20)	5(25)
Digestive				2(10)	1(5)	2(10)	1(5)
Nervous		2(10)	1(5)	3(15)	1(5)	1(5)	1(5)
Respiratory		1(5)					
Skin and appendages				1(5)		1(5)	
Special senses	2(10)	1(5)		3(15)		3(15)	3(15)
Urogenital				1(5)			
Vascular(extracardiac)							1(5)

Source: Vol.1, Page 1.164

**Frequency of Adverse Events**

For the 80 subjects who received OptiMARK, the most frequently reported adverse events were taste perversion 9/80 (11.3%), warm sensation 6/80 (7.5%), **dizziness 4/80 (5%), and headache 3/80 (3.8%)**. The frequency of all other events was <2.5%. The breakdown of the most frequent events by method of injection and injection rate is shown in Table 2. The number of subjects experiencing at least one adverse event by body system and treatment is summarized in Table 3.

Injector type	Hand	Power		Power		Power	
Treatment	OptiMARK	OptiMARK	Saline	OptiMARK	Saline	OptiMARK	Saline
Rate (ml/sec)	2	2		4		6	
Number	4	6	6	13	5	16	12
Taste Perversion	2	1	0	3	0	3	3
Warm Sensation	1	1	0	1	0	3	1
Headache	0	1	2	1	1	1	3
Dizziness	0	1	0	3	1	0	1
Other	1	2	4	5	2	7	8

Source: Vol.1, Page 1.166

Injector type	Hand	Power		Power		Power	
Treatment	OptiMARK	OptiMARK	Saline	OptiMARK	Saline	OptiMARK	Saline
Rate (ml/sec)	2	2		4		6	
Number	4	6	6	13	5	16	12
<b>Body System</b>							
Any Event	2(10)	5(25)	5(25)	9(45)	4(20)	10(50)	8(40)
<b>Application Site Disorders</b>							
Injection Site Pain			1(5)			2(10)	1(5)
Injection Site Reaction			2(10)		1(5)		
<b>Body as a Whole</b>							
Abdominal Pain						1(5)	
Arm Discomfort/Pain					1(5)		
Back Pain				1(5)			
Headache		1(5)	2(10)	1(5)	1(5)	1(5)	3(15)
Warm Sensation	1(5)	1(5)		1(5)		3(15)	1(5)
<b>Central and Peripheral Nervous System Disorders</b>							
Dizziness		1(5)		3(15)	1(5)		1(5)
Paraesthesia		1(5)	1(5)			1(5)	

<b>Gastrointestinal System Disorders</b>							
Diarrhea						1(5)	
Mouth Dry							1(5)
Nausea				1(5)	1(5)	1(5)	
Vomiting				1(5)		1(5)	
<b>Respiratory System Disorders</b>							
Epistaxis		1(5)					
<b>Skin and Appendages Disorders</b>							
Pruritus				1(5)			
Rash						1(5)	
Skin Cold Clammy						1(5)	
<b>Special Senses, Other Disorders</b>							
Micturition Frequency				1(5)			
<b>Vascular (Extracardiac) Disorders</b>							
Flushing							1(5)

Source: Vol.1, Page 1.166

Of the 140 subjects who received study drug or control, 3 subjects experienced adverse events that required corrective treatment. One subject (saline, 6 mL/sec) received acetaminophen for a mild headache, another subject (OptiMARK, 4 mL/sec) received Tylenol (Extra Strength) and aspirin for mild headaches, and the third subject (OptiMARK, 4 mL/sec) was treated with a heating pad for moderate back pain.

Of the 64 adverse events reported in this study, 40 (40/64, 62.5%) events reported by 30 subjects were considered likely to be treatment related. Of the 40 events considered likely to be related to treatment 26 (26/40, 65%) were in subjects receiving OptiMARK. Therefore, there were twice as many adverse events in the OptiMARK arm than in saline arm of this trial. Of note, there were twice as many cases of dizziness in the OptiMARK group than in saline group.

Within the OptiMARK groups, 3 events (3/4, 75%) were reported by 1 subject in the 2 mL/sec, hand held group, 3 events (3/6, 50%) were reported by 2 subjects in 2 mL/sec, Power Injector group, 9 events (9/14, 64.3%) were reported by 7 subjects in the 4 mL/sec, Power Injector group, and 11 events (11/16, 68.3%) were reported by 8 subjects in the 6 mL/sec, Power Injector group. Within the Saline Power Injector groups, 3 events (3/6, 50%) were reported by 3 subjects in 2 mL/sec group, 3 events (3/5, 60%) were reported by 3 subjects in the 4 mL/sec group, and 8 events (8/12, 75%) were reported by 6 subjects in the 6 mL/sec group. Thus, there is a roughly direct relationship between the injection rate and frequency of reported adverse events in both the OptiMARK and saline arms.

Out of 80 subjects administered Optimark, only 2 subjects reported pain at the injection site. There were no reports of extravasation.

**Thus, no serious adverse drug events were observed, but the cardiac data were not adequately analyzed.**

**The sponsor did not consider any of the abnormal vital signs, chemistry and hematology findings, although numerous, as shown below, to be an adverse event.**

**The safety and adverse event profiles based on the data from the current submission were found comparable with the current labeling.**

#### **Vital signs**

From the measured vital signs only blood pressure showed clinically significant changes in a noticeable number of subjects. It mainly manifested as a **decrease** in diastolic and/or systolic blood pressures in 4 hours after injection. They occurred in **21% subjects for diastolic BP** and 12.5 % for systolic blood pressure (Table 12.5.1-2, 1.180). About a half of that rate was reported for subjects with saline. This appears to reflect the statements throughout the submission that the cardiologist reviewing the results observed "... hypotension". A dose response relationship is not apparent, but the number of subjects was not high enough to evaluate it sufficiently.

#### **Clinical Laboratory Evaluation**

##### **Lack of direct measurement of gadolinium**

Since the toxic effects of heavy metals are well known, assesment of potential toxicity of a gadolinium MRI imaging agent can be made most directly by measuring free, chelated, or bound **gadolinium in body fluids. No such evaluation was attempted in this submission.** In absence of gadolinium measurements, the presence of free gadolinium could be estimated by its likely effect on metabolism and elimination of other metals, most notably Fe, Cu, Zn and Mg. **Since no measurement of gadolinium or other metals in urine was done, only the blood content of other metals may be suggestive.**

##### **Metals in blood**

Table 4 shows instances where the blood content of Fe, Cu, Mg and Zn changed more than 80% of the reference range either 2 or 24 hours post dose. **The decreases at 2 hours were seen for Mg, Cu and Zn, while there were increases for Fe.** How trustworthy are these data is unknown, since some of these changes occurred also in saline controls.

**Table 4. Summary of Laboratory Parameter Changes >80% of the References Range N (%) at either 2 or 24 hours Post Dose**

Injector type	Hand		Power				Power				Power			
Treatment	OptiMARK		OptiMARK		Saline		OptiMARK		Saline		OptiMARK		Saline	
Rate (ml/sec)	2		2				4				6			
Change	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec
<b>Chemistry</b>														
CPK														1(5)
Direct Bil.				1(5)										1(5) 1(5)
Glucose	8(40)		9(45)		5(25)		10		5(25)		8(40)		6(30)	
<b>Metals</b>														
Calcium	2(10)		1(5)	1(5)			2(10)		1(5)		1(5)			
Copper								1(5)				1(5)		
Iron			1(5)	2(10)			3(15)						1(5)	3(15)
Magnesium				1(5)				1(5)						
Potassium	2(10)	1(5)		1(5)			3(15)		1(5)		2(10)	2(10)		3(15) 2(10)
Zinc				2(10)										
<b>Hematology</b>														
Basophils		2(10)	3(15)	2(10)	1(5)	1(5)	2(10)	2(10)	2(10)	1(5)	3(15)	1(5)	2(10)	1(5)
Eosinophils	2(10)	8(40)	5(25)	6(30)	4(20)	5(25)	3(15)	5(25)	4(20)	7(35)	4(20)	6(30)	4(20)	3(15)
Lymphocytes		4(20)		2(10)		1(5)		2(10)	2(10)	1(5)		3(15)		2(10)
Monocytes		5(25)	1(5)	7(35)	1(5)	3(15)		3(15)		1(5)	1(5)	3(15)	1(5)	3(15)
Neutrophils	2(10)						1(5)		1(5)	1(5)				2(10)
RBC					1(5)									
<b>Urinalysis</b>														
Urine pH	2(10)		1(5)						1(5)		1(5)		1(5)	
Urine RBC													1(33)	2(67)
Urine WBC													1(33)	

Source: Vol.1, Page 1.174

**Potential interference of gadolinium with measurements of serum metals**

A potential **gadolinium interference** with measurements of other metals by specific methodologies is a debated issue. In this submission it was discovered to interfere **with the**

**calcium assay** and confirms a note in the section on Laboratory Test Interactions in the labeling. The effect of gadolinium in detection of other metals whether directly on assays, or otherwise, would suggest the presence of free gadolinium. As no urine data is available, the specifics in regard to OptiMARK remain to be established.

**Hepatic and renal function tests**

Likewise, in the absence of other laboratory data, it appears that there is a generalized effect of OptiMARK injection to interfere with normal liver function, as demonstrated **by a combination of statistically significant decreases in numerous parameters** such as ALT, AST, albumin, ALP, CPK, LDH, total protein as well as an increase in bilirubin (Table 5). This is manifested mainly 2 hours post injection. The clinical relevance of these decreases is unknown at this time. Although the effect on renal function does not start until 24 hours post injection, a statistically significant increase in BUN is hard to overlook as it occurs in a number of treatment groups. A separate, but related, concern should be **a decrease in phosphorus (P) which occurs in all groups without an exception (including saline) at both 2 and 24 hours**. A heavy metal effect on bone may be one of the explanations. Beyond 24 hrs, there is no reference to potential follow-up of the abnormal clinical chemistry values to resolution.

<b>Table 5. Summary of Statistically Significant Changes From Baseline for Laboratory Parameters By Time Period and Treatment-Standardized Values – Mean (SD)</b>							
Injector type	Hand	Power		Power		Power	
Treatment	OptiMARK	OptiMARK	Saline	OptiMARK	Saline	OptiMARK	Saline
Rate (ml/sec)	2	2		4		6	
<b>2 Hours Post Dose</b>							
<b>Chemistry</b>							
ALT			-1.6(2.8)			-1.8(3.1)	-1.8(3.1)
Albumin	-4.3(8.0)	-6.3(9.2)	-5.3(9.7)	-8.5(10.8)	-4.5(8.4)		
ALP	-5.1(4.6)	-4.2(4.3)	-2.3(4.8)	-5.5(4.6)	-3.0(4.3)		-5.0(5.2)
AST		-3.5(5.0)	-3.0(3.6)		-2.0(3.7)		
Cholesterol	-5.6(9.8)	-6.3(7.3)	-5.4(7.4)	-9.1(10.8)	-5.4(7.5)		-6.0(10.7)
CPK	-2.0(2.7)		-3.2(4.3)	-4.4(4.9)	-2.2(2.3)	-1.1(2.1)	-2.6(3.9)
Creatine		-3.0(6.3)					
Direct Bilirubin					11.7(16.3)		
Glucose	53.5(53.4)	61.5(50.4)	47.3(50.6)	73.3(65.4)	48.4(43.9)	56.8(52.0)	63.9(52.4)

LDH	-3.6(7.5)		-6.3(8.9)	-6.4(6.1)			-3.3(6.1)
Phosphorus	-26.1(19.3)	-25.7(22.5)	-25.3(14.9)	-19.3(15.1)	-23.7(20.0)	-19.3(18.6)	-19.3(14.3)
Total Bilirubin	7.5(7.9)	5.0(6.9)	7.5(7.9)		6.5(6.7)		7.0(8.0)
Total Protein	-6.9(12.0)	-9.6(13.7)	-7.9(12.0)	-13.1(19.4)	-6.0(10.0)		-6.0(12.8)
Urea Nitrogen	-12.5(9.1)	-12.0(7.0)	-12.5(9.1)	13.0(9.2)	-12.5(7.9)	-11.0(8.5)	-10.5(8.9)
Uric Acid							
<b>Metals</b>							
Calcium							
Copper	-4.6(9.2)						
Iron				17.2(20.3)	13.3(18.0)		9.7(18.4)
Magnesium	-16.3(32.7)	-28.8(34.7)	-13.8(23.6)	-20.0(26.4)	-13.8(17.2)	-15.0(24.9)	-23.7(24.3)
Potassium		-33.3(39.6)	-21.7(44.8)				
Sodium							-9.5(13.2)
Zinc	-33.9(19.0)	-37.6(22.8)		-28.7(19.3)			-34.2(17.2)
<b>Hematology</b>							
Bands				5.6(10.3)			
Eosinophils							
Lymphocytes	-34.0(41.4)	-24.5(33.3)	-19.3(29.0)	-28.8(41.5)		-27.5(41.5)	
Monocytes	-37.9(44.0)	-27.1(45.2)	-30.7(36.9)	-26.4(44.0)	-20.7(32.6)		-20.7(41.3)
Neutrophils	35.8(27.4)	25.5(23.2)	23.7(23.0)	28.5(30.2)	17.2(30.8)	24.0(30.6)	16.0(29.1)
Hematocrit				-9.9(17.7)			-11.9(16.9)
Hemoglobin	-9.8(18.6)	-8.0(13.1)		-10.5(17.1)			-8.7(15.1)
Platelets	-3.6(6.9)	-5.1(5.9)		-6.0(9.4)	-1.7(3.0)	-3.9(7.0)	
RBC	-11.3(18.7)	-7.2(13.8)		-13.3(19.9)	-7.5(15.3)	-13.8(17.8)	
WBC						-6.9(9.7)	
<b>Urine</b>							
pH	28.3(30.2)	18.3(31.0)	18.3(24.1)	18.3(27.0)	20.0(30.9)	28.3(26.6)	27.5(33.9)
Specific Gravity		11.1(19.4)				11.2(21.8)	
<b>24 Hours Post-Dose</b>							
Chemistry							
Albumin							5.5(10.8)

ALP	-3.8(5.7)	-1.8(3.7)		-3.4(5.6)		-4.0(6.8)	
AST		-4.0(5.9)					
CPK	-7.6(6.5)		8.7(10.3)	-15.6(23.5)	-10.5(13.9)	-9.8(11.9)	-5.2(4.9)
Creatine			-3.3(6.5)				
Glucose		-8.3(15.3)	-10.2(15.2)		-8.3(11.1)	-7.1(14.1)	-14.1(14.5)
LDH			-5.4(8.8)	-5.8(9.2)			
Phosphorus	-13.3(15.8)	-11.2(16.1)	-11.2(9.2)	-8.3(15.0)	-9.2(15.3)	-9.5(12.8)	-7.3(13.7)
Urea Nitrogen	11.5(20.6)	13.0(19.2)	9.5(17.3)			10.0(14.9)	
Uric Acid	-8.6(7.8)	-9.5(5.1)	-8.2(6.9)	-12.5(16.2)	-12.2(8.9)	-6.3(8.5)	-9.5(12.3)
<b>Metals</b>							
Calcium	18.8(39.4)		18.9(33.0)				14.5(20.8)
Iron	-11.5(23.4)						
Potassium				14.9(20.5)			
<b>Hematology</b>							
Eosinophils	-31.7(67.1)						
Lymphocytes	-22.3(41.8)	-24.0(42.9)		-23.8(38.0)			
Neutrophils	21.8(29.2)	20.8(26.1)	11.3(20.1)	21.5(27.9)			
Platelets						-4.7(7.7)	-5.4(10.3)

Source: Vol.1, Page 1.175

#### Hematology

A **generalized effect, reminiscent to the effect on liver parameters**, can also be observed from a combination of changes in hematologic parameters. Statistically significant decreases at 2 hours can be seen simultaneously in numerous treatment groups for lymphocytes, monocytes, platelets as well as hemoglobin and hematocrit, while an increase was found for neutrophils (Table 5). The effects in the same respective directions extended to 24 hours for lymphocytes, eosinophils and platelets as well as neutrophils. Once again, beyond 24 hrs, there was no reported reference to a potential follow-up of abnormal values to resolution.

#### Validity and impact of laboratory studies

For various laboratory parameters, **the direction of a change is almost always the same across different treatment groups**. That would tend to favor and amplify the conclusions made. Somewhat disturbing, however, is the fact that saline, which is presumed to be clinically inconsequential, exhibits numerous associated abnormalities in this study. The sponsor did not comment on possible reasons, but took the saline results at face value. The sponsor then

exploited these spurious findings to support the argument that the safety profiles of OptiMARK and saline are similar, which is unlikely. Rather, inaccuracies of the assays or investigator's accepted normal ranges are among possible reasons.

## 7.1 SAFETY UPDATE

Upon request the sponsor submitted a line listing of adverse events that have occurred with marketed product since the date of this supplement. This short 4-page report is unremarkable, except for 2 reports of seizures and one case of near seizure in a span of 6 months in 2002.

All these three cases were referred to NDA # 20-976 which is for a Pharmacy Bulk Pack. MedWatch report forms were provided by the sponsor for the two cases. The third case of a near seizure was misidentified in the sponsor's report where the potential concern about seizure was omitted and only nausea, light-headedness, increased saliva, pruritus vasodilation, headache and hypoaesthesia were mentioned. No MedWatch report form was provided on this case by the sponsor.

However, the MedWatch report on the latter case was contained among others in the ODS Post Marketing Safety Review received in response to a 11/14/02 request. This 30-year old subject was administered oxygen as a part of treatment and was transferred to hospital where he was observed for several hours. He developed right-sided numbness and on that note the report ends.

The other two reported cases of seizures mentioned earlier were a 38-year old woman and a 52-year old man. Yet another case of seizures was reported in the OPDRA report, but that occurrence happened in 2001. Up to now, seizure has not been listed as an adverse event in the label and the respective change should be implemented.

## 8. DOSING, REGIMEN AND ADMINISTRATION ISSUES

The study found minor differences in expected directions between saline and Optimark as well as among OptiMARK injections administered at increasing rates, however, the study was not designed, executed and analyzed well enough to detect true differences, if present.

If the sponsor intends to pursue administration for OptiMARK by power injector at higher rates, the study should involve much greater number of subjects and the trial should be executed in such a way that all critical data are obtained. The data should then be analyzed by a generally accepted methodology in order to obtain reliable, non-ambiguous results.

## 9. USE IN SPECIAL POPULATIONS

### 9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race or Ethnicity. Comments on Adequacy of the Applicant's Analyses

N/A

9.2 Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

N/A

9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

N/A

## 10. CONCLUSIONS, RECOMMENDATIONS AND LABELING

### 10.1. Conclusions Regarding Safety and Efficacy

The study found minor differences in expected directions between saline and Optimark as well as among OptiMARK injections administered at increasing rates, however, the study was not designed, executed and analyzed well enough to detect true differences, if present. The safety and adverse event profile found in this review was comparable with current labeling with the following exception. The safety update revealed that seizures may be associated as an adverse event with the administration of Optimark.

### 10.2. Recommendations on Approvability

Optimark may be used with the power injector at rate 2 ml/sec, the rate for which it is currently approved.

### 10.3. Labeling

As a result of safety update analysis, labeling should be changed to include seizures as adverse event. Eighty normal volunteers were studied using Optimark administered by a power injector and the safety profile was found not to be different from that of patients.

#### References:

1. Boland LM, Brown TY, Dingleline R. Gadolinium block of calcium channels: influence of bicarbonate. Brain Research 1991; 563:142-50.
2. Scheer HW, Rosenthal LP and Collier B. Effects of alpha-lantrotoxin, lanthanides and elevated potassium concentrations on acetylcholine release and free intracellular calcium levels in rat cerebellar cortex synaptosomes. Neurochem Int 1991; 18:115-24.
3. Hardonk MJ, Dijkhuis FWJ, Hulstaert CE, Koudstaal J. Heterogeneity of rat liver and spleen macrophages in gadolinium chloride-induced elimination and repopulation. J Leukocyte Biol 1992: 52:296-302.

4. Zhong Z, Goto M, Hijioka T, Oide H, Kaufman FC, Thurman RG. Role of Kupffer cells in storage and metabolism of benzo(a)pyrene in the liver. *Drug Metabolism and Disposition* 1994; 22:680-87.
5. Koudstaal J, Dijkhuis FWJ and Hardonk MJ. Selective depletion of Kupffer cells after intravenous injection of gadolinium chloride. In: *Cells of Hepatic Sinusoid*, Eds. Wisse E, Knook DL, McCuskey RS, Kupffer Cells Foundation, P.O.Box 430, 2300 AK Leiden, The Netherlands, 1991; 3:87-91.
6. Hu H, Sachs F. Mechanically activated currents in chick heart cells. *J Membrane Biol* 1996, 154:205-16.
7. Kasokat T, Urich K. Quantitation of dechalcation of gadopentatate dimeglumine in rats. *Arzneim-Forsch/Drug Res* 1992;6:869-876.
8. Puttagunta NR, Gibby WA, Smith GT. Human in vivo comparative study of zinc and copper transmetallation after administration of magnetic resonance imaging contrast agents. *Invest Radiol* 1996; 31:739-41.
9. Nordenbo AM, Somnier FE. Acute deterioration of myasthenia gravis after intravenous administration of gadolinium-DTPA. 1992;340:1168. Letter to the Editor.

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Joseph Zolman  
1/31/03 03:59:10 PM  
MEDICAL OFFICER

Sally Loewke  
1/31/03 04:12:43 PM  
MEDICAL OFFICER  
See Division Memo dated 1/31/03