CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20937

MEDICAL REVIEW(S)

Serial Number:	A2
Type of Submission:	Class 2 Resubmission
NDA/IND number:	20937/41,534
Letter date:	June 7, 1999
Date Review Completed:	September 29, 1999 (Addendum November 29, 1999 as Attachment 2)
Sponsor:	Mallinckrodt Inc. St. Louis, MO
Review team:	CSO –Moore; Biopharm – ; Chemistry – Place; Pharmtox – Melograna; Statistics –Davi; Clinical – Raman/Loewke
Related INDs/NDAs:	IND NDA 20975, NDA 20976, NDA 20975

BACKGROUND, OUTLINE AND MATERIAL REVIEWED:

This NDA was submitted in February 1998 and reviewed (CNS efficacy and overall safety) in November 1998. In December1998, a "not approval" letter (included clinical concerns) was issued based on deficiencies and lack of sufficient analyses of the ECG (electrocardiographs) safety database (see letter dated Dec 23, 1998). The primary focus of concern was the use of rather liberal parameters by the sponsor to designate abnormalities in ECGs. Additionally, there were concerns on the adequacy of the database and its interpretation (including appropriate qualifications of the reader/s). The initial ECG comments (pages 185 to 192) have been attached (attachment 1 in this review; repaginated pages 1 through 7). The ECG safety database has been re-analyzed (using more acceptable normal parameters) by the sponsor and has been resubmitted for review. This submission consists of volumes 3.1 to 3.27 of which volumes 3.10 to 3.27 contain clinical ECG related information. Additional related submissions include (N000BM); (NC); (BM); (C); (AZ). No new data has been included in this submission. There are no new safety concerns reported since the initial submission according to the sponsor (p. 1.168, vol. 3.1). It is worth noting at this time that the data in appendix 26 (CD-ROM with patient database) and the data in appendix 27 (patient profiles) are different because the latter data is "derived" from the electronic database by the sponsor. Emphasis has therefore been placed on the raw data from the CD-ROM. Reference is made to the initial review and the initial NDA submission when appropriate. For purposes of completeness and relevance, the following information on Chemistry, Pharmacological Category, Proposed Indication, Proposed Dosage and Administration, Extent of Exposure and Trials, Subject/Patient Disposition and Demographics are reiterated.

BACKGROUND INFORMATION ON THE DRUG

General:

The "active ingredient" in OptiMARK™ is a complex consisting of gadolinium (+3) and the chelating agent versetamide. Gadolinium is a paramagnetic ion, which enhances the

relaxation rates of immediately surrounding water when placed in a magnetic field thereby increasing brightness when T1-weighted magnetic resonance imaging is performed. OptiMARK™ does not cross the intact blood-brain barrier.

Drug: {for full details, please refer to the Chemistry Review by Dr. Place}
Trade Name: OptiMARK™
Generic 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
Empirical Formula: $C_{20}H_{34}N_5O_{10}Gd$
Description: non-ionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide). The table below summarizes some of the physico-chemical properties of OptiMARK.

SAFETY: PHYSICO-CHEMICAL PROPERTIES: NDA # 20 937-OptiMARK™	
Component	**Concentration (mg/ml)**
gadoversetamide	330.9
versetamide	
calcium hydroxide	
calcium chloride dihydrate	
sodium hydroxide	as required
hydrochloric acid	as required
Property	**Feature**
Appearance	clear, colorless to pale yellow solution
Sterility	sterile, nonpyrogenic
pH	5.5 - 7.5
Osmolality	(3.9 times that of plasma)
Viscosity	2.0cP at 37°C 3.1cP at 20°C
Density	1.160g/ml at 25°C
Concentration	0.5M [= 0.5 mmol/ml]

PHARMACOLOGIC CATEGORY

OptiMARK is a gadolinium-containing intravenous contrast agent for magnetic resonance imaging. The table below summarizes some of the pharmacological properties of OptiMARK.

NDA # 20 937-OptiMARK™: SAFETY: CLINICAL PHARMACOLOGY: HALF-LIFE, DISTRIBUTION, ELIMINATION*		
mean distribution (mean ± SD)	*13.3 ± 6.8 minutes*	
elimination half-life (mean ± SD)	*103.6 ± 19.5 minutes*	
volume of distribution at steady state	*162 ± 25 mL/kg (normal subjects; equivalent to that of extracellular water)*	
renal clearance rate	*69 ± 15.4 mL/hr/kg*	
plasma clearance rate	*72 ± 16.3 mL/hr/kg*	
Population	*Elimination Half-Life (hours)*	
	Men	*Women*
healthy volunteers	*1.73 ± 0.31*	*1.73 ± 0.40*
normal patients	*1.90 ± 0.50*	*1.88 ± 0.47*
renally impaired	*8.74 ± 5.14*	*6.91 ± 2.46*
hepatically impaired	*2.09 ± 0.03*	*2.35 ± 1.09*

**From NDA submission: "Table 2: Elimination Profiles ..." [p. 1.0208, Vol. 2.1]*

PROPOSED* INDICATION

[*As proposed by the Sponsor; from the Package Insert initial NDA submission]

- The **proposed indications** for OptiMARK™ are: [p. 1.0348, Vol. 2.2]

PROPOSED* DOSAGE AND ADMINISTRATION

[*As proposed by the Sponsor; from the Package Insert]

EXPOSURE AND TRIALS

- A total of 1309 patients received OptiMARK™ of which 354 patients had two doses giving a total number of 1663 exposures. In addition, there were 329 patients who received Magnevist® and 46 patients or subjects who were given placebo.
- The total number of studies contributing to this NDA is 19. Of these, there are five Phase 1 studies (including one study conducted in Japan; the Sponsor stated that the safety data for this could not be integrated with those of the four US studies), six Phase 2 studies, and eight Phase 3 studies. Of the eight Phase 3 studies, "Two open-label CNS studies (Study 484 and 485) and two open-label liver studies (Study 486 and 487) were terminated prior to completion of enrollment in order to incorporate the FDA-suggested study design modifications including a comparator group (i.e., Magnevist®) and overall analytical plan to demonstrate equivalence to the approved comparator"[p. 1.0378, Vol. 2.2]. Of the remaining four Phase 3 studies, Studies 488, 525, 490, and 526 "... were similar in design with common clinical safety monitoring (vital signs, physical exams, ECG's, clinical laboratory parameters, injection tolerance and adverse events) and with generally similar inclusion and exclusion criteria." [p. 1.0379, Vol. 2.2]

DEMOGRAPHICS

- There was a total of 1684 patients/subjects enrolled in all studies of which 1309 were given OptiMARK™ (total of 1663 injections as 354 patients received two doses), 329 were given Magnevist®, and 46 received placebo.
- Of the total 1684 patients/subjects, 870 (52%) were men and 814 (48%) were women; 1718 (84.3%) were White, 183 (9%) were Black, 48 (2.4%) were Asian, and 89 (4.4%) were Others.
- In the OptiMARK™ group, 680 (52%) were men and 629 (48%) were women; the average age was 49.4 years [p. 26.0057, Vol. 2.147]. In the Magnevist® group, 165 (50%) were men and 164 (50%) were women; the average age was 51.4 years. In the placebo group, 25 (53%) were men and 21 (47%) were women; the average age was 44.4 years. Additional information is provided in the "Demographic Overview Table" below.

SAFETY: DEMOGRAPHIC OVERVIEW: OptiMARK™

Parameter	OptiMARK™	Magnevist®	Placebo
Total Number (%)	1309 (~78%)	329 (~19%)	46 (~3%)
Mean Age (years)±SD [Range]	49.52 ± 14.95 [12 - 85]*	51.4 ± 14.8 [20 - 86]	44.4 ± 13.0 [21 - 73]
Sex: number (%)			
- Male	680 (52%)	165 (50%)	25 (54%)
- Female	629 (48%)	164 (50%)	21 (46%)
Race: number (%)			
- White	1102 (84%)	268 (81%)	41 (89%)
- Black	116 (9%)	35 (11%)	5 (11%)
- Asian	33 (3%)	11 (3%)	0 (0%)
- Others	58 (4%)	15 (5%)	0 (0%)
Mean Height(cm)±SD [Range]	170.3 ± 10.1 [120 - 208]	170.4 ± 10.3 [140 - 196]	171.9 ± 8.9 [156 - 190]
Mean Weight(kg)±SD [Range]	75.35 ± 16.28 [38 - 145]	76.6 ± 17.3 [42 - 141]	81.4 ± 19.6 [52 - 153]
Mean BSA (m^2) ±SD [Range]	1.88 ± 0.23 [1.22 - 2.68]	1.90 ± 0.3 [1.4 - 2.7]	2.0 ± 0.2 [1.5 - 2.7]

[Data from NDA submission: pp. 26.0058 - 26.0059, Vol. 2.147]

~ Reviewer's Comment: On p. 1.0348, Vol. 2.2 (and in the proposed labeling section), the Sponsor states, "A total of 2038 subjects or patients were exposed to study drug or placebo ...". The actual breakdown is:

1309 OptiMARK™ (number of patients = 1309, number of exposures = 1663 because 354 patients received two doses-phase 2, #s-464, 465, 466, 467, 468, 469) → these are the critical numbers

329 Magnevist®

46 placebo

→ 1684 subjects participating in studies and 2038 is total number of exposures to any agent (i.e. OptiMARK™+ placebo + Magnevist®).

*Further clarity is required in the **labeling** section to reflect these numbers appropriately.*

- The table below summarizes the overall exposed patient disposition by treatment: (OptiMARK™, Magnevist® or Placebo)

SAFETY:OVERALL=EXPOSED/DISPOSITION/DOSE/AE: NDA # 20 937-OptiMARK™									
	OptiMARK™ mmol/Kg							Magnevist® mmol/kg	Placebo
	0.1	0.2	0.3	0.4	0.5	0.7	Combined	0.1	
Entered	986	205	229	24	263	4	1711	337	46
Dropped pre-dose	27	4	8	2	7	0	48	8	0
Exposed/Safety evaluation	959	201	221	22	256	4	1663*	329	46
Serious Adverse events	5	See Serious adverse events below and comments in individual trials					8	2	0
Deaths	1	0	0	0	0	0	1	0	0
Patients with one or more adverse events	281 (29.3%)	See Adverse events below and comments in individual trials					510 (30.7%)	114 (34.7%)	22 (47.8%)
Patients with no events	678 (70.7%)	No comments					1153 (69.3%)	215 (65.3%)	24 (52.2%)
Dropped post-dose	3	0	5	0	4	0	12	0	0
Dropped for Adverse Event	0	0	2	0	2	0	4	0	0
Actual subjects/patients							1309*	337	46

*Note: See comments on previous page on demographics
This table has been corrected (to reflect the actual numbers) since the initial NDA submission and review (ref. Letter 10-28-99)

Subsequent review comments on the ECG safety data that follows is discussed under:

I. Adequacy of the data
II. Findings
III. Summary
IV. Conclusions
V. Labeling Recommendations
VI. Recommendations

I. ADEQUACY OF ECG SAFETY DATA:

The adequacy of the safety ECG data of this drug program can be assessed under the following broad categories:

A) Adequacy of Pre-Clinical Safety Data and
B) Adequacy of Clinical Safety Data

A) ADEQUACY: PRE-CLINICAL

Generally, the adequacy of the pre-clinical safety ECG data for any drug (including OptiMARK) can be addressed in terms of:

1. *In vitro* studies (Cardiac Ionic Current studies, Cardiac Action Potential Duration studies, etc.)

2. Screening Animal model studies (Hemodynamic Studies, Electrocardiographic Studies, etc.) and focused preclinical studies (for proarrhythmia) when necessary.

Repolarization-altering drugs that are associated with malignant ventricular arrhythmias tend to affect repolarization by blocking specific ionic currents (such as the delayed-rectifier current I_{Kr}), in cardiac cells. The effects of OptiMARK on ion channels (especially I_{Kr}) and on action-potential duration (in vitro) have not been studied.

The pharmacology and toxicology review of OptiMARK (Page 109 of the pharm-tox review by John Melograna) on the initial NDA submission highlights the findings of hemodynamic and electrocardiographic safety studies. There were transient dose-related decreases in heart rate, arterial blood pressure (mean, systolic and diastolic), and left ventricular systolic pressure. In these studies, blood pressure dropped without a compensatory increase in heart rate. Random arrhythmias and premature ventricular conductions (PVCs) were reported by the sponsor and given the nature of the study design, definitive conclusions could not be drawn on this issue. There were no reported PR or QT interval changes. Given the similarities between OptiMARK and the other approved gadolinium agents, it was felt (at that time) that there was no need for further cardiac safety studies.

I.B ADEQUACY - CLINICAL

Adequacy of Clinical Safety Data can be assessed in terms of:

1. Number of Exposures- were enough number of subjects exposed to the drug?
2. Number of Readings/recordings- were there enough number of complete tracings enabling to make an assessment?
3. Reader/Interpreter Qualifications- cardiologist or not? (this issues has been addressed by the sponsor and an independent cardiologist's re-analyzed report has been included in this submission)
4. Dose Ranging Studies- to address any dose related effects (of concern in repeat dosing as well)
5. Measured Intervals- were all the intervals, in particular QT/QTc, measured?
6. Acceptable normal parameters for measured intervals- were the chosen normal range/s acceptable? (this has been addressed by the sponsor and has been incorporated in this submission)
7. Time Points and Duration- were the time points and the duration of measurements appropriate with reference to the metabolism of the drug?
8. Enrollment- was the studied patient population appropriate and a representative population or was there a bias?
9. Concomitant medications- was the effects of other concomitant medications and drug-drug interaction/s studied?

This re-submission is similar to the initial submission with respect to the actual data (does not contain new data or inclusions), but has been presented using more acceptable normal range for the measured parameters (of the intervals) and in a clinically meaningful and interpretable fashion. Attachment 1 (enclosed) comprehensively addresses some of these issues. When comparison is made to the comments made in the original NDA review (Attachment 1- deficiency table page 2, timing table page 3) and the currently presented data as summarized in the table below, there are several similarities including the projections on the useable data.

OptiMARK 20937: SAFETY: ECG: ADEQUACY BY DOSE, EXPOSURES, TIME POINT(S), INTERVALS, READER, READINGS

Phase	Study #	Reader (Cardiologist)	Dose (mmol/kg)	Exposed (N)	Completed[A] Readings (N)	Time Point/s (post dose)	Intervals (measured)	Comments
3 (open label)	484/485	~48%	0.1	49	48	24 hours	PR QRS	No QT/QTc measured No earlier timings No monitoring during dosing
			0.3	5	5			
3 (open label)	486/487		0.1	99	99			
			0.2	121	121			
3 (pivotal)	488	? (~ 75% by internist and cardiologist)	0.1	133	133		PR QRS QT/QTc	No earlier timings No monitoring during dosing
3 (pivotal)	490		0.1	98	98			
3 (pivotal)	525		0.1	129	129			
3 (pivotal)	526		0.1	100	100			
1	489	? (~ 79% by internist and cardiologist)	0.1[C]	40	40[B]	Immediate 15 minutes 30 minutes 1 hour 2 hour 24 hour	PR QRS QT/QTc	No monitoring during dosing
			0.3	42	42[B]			
			0.5	39	39[B]			
1	538		0.1[C]	54	54[B]			
1	543		0.1	8	8	1 hour		

Ref: Letter Nov. 12 and Dec 3 1998, Vol. 3.1, 3.10

A= Defined by the sponsor (Ref: Letter Nov 12, 1998) as those ECGs that were "interpreted" = Manual (by personnel) + Automated (interpreted by machine but later over read (with or without changes) by readers. Not included were those that were automated without over reads and those without initials by readers.

B= A total of 175 (40+42+39+54) patients/subjects were the only ones in this entire program to receive ECG monitoring at more frequent intervals (shaded area).

C= A total of 94 (54+40) patients/subjects of these 175 received the proposed labeling dose of 0.1mmol/kg (shaded area).

Summary: The following conclusions can be drawn on adequacy (clinical):

- There was no ECG data collected in the first-in-human study # 433 in this program, in which doses as high as 0.7mmol/kg was administered.
- ECG safety data for Phase 1 study # 1177 (Japanese study) is not included. It is worth while to reiterate that there was bradycardia and hypotension noted in some of the enrolled normal male volunteers in this study (please refer to the comments in the NDA review on this protocol/study, pp. 23-33).

- The effects of concomitant medications and drug-drug interactions were not studied in this program.
- There was no monitoring during dosing in any of the studies.
- Studies 489 and 538 are the only two studies which incorporate more frequent time points at which ECGs were obtained, and when QT/QTc was measured, thereby making these two studies the "the back bone" upon which the data rests (if any meaningful interpretations can be made). Bulk of the data was collected only at 24 hours following dosing (for all the other studies). This latter data (at 24 hours) is relatively less meaningful and less informative in addressing the effects of OptiMARK, given its metabolism. As noted above (page 3- exposure and trials) a total of 1309 patients received OptiMARK™ of which 354 patients had two doses giving a total of 1663 exposures. Whether any meaningful safety conclusions can be drawn when the "merited" recordings/data (all parameters and at frequent time points) is on 175 subjects (see shaded area in adequacy table above), is a concern. Additionally, the proportion of these 175 patients' records (with "merited" data) that were read by cardiologist/s is unknown (sponsor states ~ 75% was read by internists + cardiologists). A significant number of the tracings (records) were interpreted by non-cardiologists. The impact of the issue of reader qualification has been buffered as the present submission includes an independent cardiologist's report on the tracings (all available tracings were re-read by an independent cardiologist).
- Similarly, whether any meaningful safety conclusions on dose ranging can be made, rests on a single study (# 489 involving 121 subjects). Although the proposed labeling calls for a dose of 0.1mmol/kg, the importance of the lack of adequate data on dose ranging would be of concern in repeat dosing, where the total dose the patient may receive in a short period may exceed the proposed 0.1mmol/kg.
- When one views the pharmacology/metabolism of OptiMARK together with the proposed dosage of 0.1mmol/kg, it is evident that the proof of the effects of OptiMARK (if any) on the heart would be present in the 94 subjects enrolled in studies 538 (with 54 subjects) and study 489 (with 40 subjects). Therefore, the focus of this EKG review has been on these 94 subjects/patients, who have relatively merited data with respect to the frequency of the time points.
- Whether the study patients included high-risk patients (for development of cardiac events) in sufficient numbers is also a concern.
- Given these concerns on the adequacy, it is apparent that the findings of the data would have a significant impact in understanding the behavior of OptiMARK with respect to the heart.

II. FINDINGS:

The effects of OptiMARK on the heart (findings; if any) may be categorized and assessed as follows:

A) Effects on ventricular systole (ventricular depolarization and repolarization) as measured by the QT/QTc interval

B) Effects on atrial depolarization and atrio-ventricular conduction as measured by the PR interval
C) Effects on ventricular depolarization as measured by the QRS interval
D) Effects on ventricular repolarization as measured by T/U wave abnormalities
E) Combined effects on PR, QRS, QT/QTc and T/U
F) Overall effects on the Rhythm

As in any clinical drug development program, the single most important step would be to assess the effect of OptiMARK on QT/QTc intervals (if any). For reasons summarized above in the adequacy section, it is lucid that such an assessment is possible only with studies 489 and 538 in this program involving ~ 175 subjects (all doses) of which 94 subjects received the proposed labeling dose of 0.1mmol/kg. Emphasis has therefore been placed on these two studies. Further comments and discussions made on to these studies may be applicable to the entire program, even though the database is narrow.

II.A EFFECTS OF OptiMARK ON VENTRICULAR SYSTOLE (DEPOLARIZATION AND REPOLARIZATION) → QT(QTc):

A prolonged QT/QTc means that there is delayed repolarization of the ventricular myocardium and this is usually associated with an increased predisposition to reentry, thus favoring the development of serious ventricular tachyarrhythmias, syncope and death. Therefore it is crucial to make this assessment in-depth.

The table on page 3 of attachment 1 gives information on the studies and the time points of data collection. Vol. 3.1 (pp. 1.032, 1.036) contains the normal acceptable values upon which the data has been re-analyzed by the sponsor. Sponsor's summary table (vol. 3.1, p. 1.105) identifies ~ 90 QT/QTc abnormalities for all studies at all time points for 0.1mmol/kg dose. Additional data is also presented in the summary table in the summary section III below.

APPEARS THIS WAY
ON ORIGINAL

The table below summarizes post dose QT/QTc changes by frequency and magnitude for all doses:

OptiMARK 20937: SAFETY: ECG: QT/QTc: POST DOSE CHANGES: ALL STUDIES TIMING, FREQUENCY, MAGNITUDE, SHIFT

Dose (mmol/kg)	Timing (post dose)	Interval (msec)	<30[C]		30-60[D]		>60		Normal Pre-dose → High post-dose Shifts[E] N (%)
			N[B]	%	N	%	N	%	
0.1	Immediate[1]	QT	91	98.91	1	1.09	0	0	1 (1.09)
		QTc[A]	92	100	0	0	0	0	3 (3.26)
	15 minutes[1]	QT	91	98.1	1	1.09	0	0	1 (1.09)
		QTc	91	98.91	1	1.09	0	0	4 (4.35)
	30 minutes[1]	QT	88	94.62	5	5.38	0	0	1 (1.08)
		QTc	92	98.92	1	1.08	0	0	2 (2.15)
	1 hr[2]	QT	93	92.08	7	6.93	1	0.99	5 (5.38)
		QTc	95	94.06	4	3.96	2	1.98	5 (5.38)
	2 hr[3]	QT	86	92.47	6	6.45	1	1.08	4 (4.30)
		QTc	89	95.70	4	4.30	0	0	4 (4.30)
	24 hr[4]	QT	365	94.32	18	4.65	4	1.03	10 (2.58)
		QTc	370	95.61	15	3.88	2	0.52	20 (5.17)
0.3[5]	Immediate	QT	40	97.56	1	2.44	0	0	1 (2.44)
		QTc	39	95.12	2	4.88	0	0	2 (4.88)
	15 minutes	QT	41	100	0	0	0	0	0
		QTc	41	100	0	0	0	0	0
	30 minutes	QT	41	97.62	1	2.38	0	0	0
		QTc	42	100	0	0	0	0	0
	1 hr	QT	39	92.86	2	4.76	1	2.38	0
		QTc	40	95.24	2	4.76	0	0	1 (2.38)
	2 hr	QT	40	95.24	2	4.76	0	0	0
		QTc	42	100	0	0	0	0	1 (2.38)
	24 hr	QT	39	92.86	3	7.14	0	0	2 (4.76)
		QTc	42	100	0	0	0	0	0
0.5[5]	Immediate	QT	38	100	0	0	0	0	0
		QTc	34	89.47	3	7.89	1	2.63	4 (10.53)
	15 minutes	QT	36	94.74	2	5.26	0	0	1 (2.63)
		QTc	37	97.37	1	2.63	0	0	2 (5.26)
	30 minutes	QT	36	94.74	2	5.26	0	0	2 (5.26)
		QTc	37	97.37	1	2.63	0	0	1 (2.63)
	1 hr	QT	35	92.11	3	7.89	0	0	0
		QTc	38	100	0	0	0	0	2 (5.26)
	2 hr	QT	35	92.11	3	7.89	0	0	0
		QTc	38	100	0	0	0	0	2 (5.26)
	24 hr	QT	36	94.74	2	5.26	0	0	1 (2.63)
		QTc	36	94.74	2	5.26	0	0	3 (7.89)

Ref: Vol. 3.11, CD ROM (Vol. 3.17) for data on <30

A= All QTc intervals calculated using Bazett's formula (QT ÷ $\sqrt{}$ RR interval in seconds$^{1/2}$)
B= Number of available "**interpretable records**" for the chosen parameter (for all Ns at all time points)
C= Further break down into <5, 5-25, and 25-30 msecs were carried out by the FDA reviewer. This revealed that the majority of changes occurred in the <5 msec group for all the time intervals.

D= 25 QTc prolongations (in this range of 30-60) were noted in the volumes and as indicated in this table. However, there were 30 QTc prolongations (in the same range) noted in the raw electronic data as indicated in the "break down" table below.
E= High pre-dose → High/Normal post-dose changes have not been included
1= Study/s 489, 538 (total enrolled/exposed 121+54=175)
2= Study/s 489, 538, 543 (total enrolled/exposed 121+54+8=183)
3= Study/s 489, 538, 468 (total enrolled/exposed 121+54+5=180)
4= Study/s 489, 538, 543, 469, 484, 485, 486, 487, 488, 490, 525, 526
5= Study 489 only (although there were other dose ranging studies in this program, either safety data was not collected at all or were incomplete or there were no QT/QTc intervals measured).

Note: The following inferences can be drawn from the presented data and the "post-dose table" above:

- 22(12) QT(QTc) prolongation ≥ 30msecs occurred with 0.1mmol/kg dose within 2 hours post dosing and 22(17) at 24 hours post dosing; combined 44(29) QT(QTc)- shaded area. That is ~50% of QT/QTc prolongation occurred within two hours post dose and ~50% occurred @ 24 hours post dose.
- 6 of these 44 had QT/QTc prolongation of ≥ 61msecs (four @ 24 hours post, one @ one hour post, one @ 2 hour post)- shaded area. However 9 subjects were identified as having QT/QTc ≥ 61msecs when the electronic data (CD-ROM) was analyzed.
- 7(4) QT(QTc) prolongation ≥ 30msecs occurred with 0.3mmol/kg dose within 2 hours post dosing and 3(0) at 24 hours post dosing; combined 10(4).
- 10(6) QT(QTc) prolongation ≥ 30msecs occurred with 0.5mmol/kg dose within 2 hours post dosing and 2(2) at 24 hours post dosing; combined 12(8).

The effects of OptiMARK on ventricular systole (i.e. depolarization and repolarization as measured by QT) may be further summarized as shown in the tables below (for all studies at all time points and for 0.1mmol/kg dose):

OptiMARK 20937: SAFETY: ECG: QT[A]/QTc[B]: DOSE 0.1mmol/kg: ALL STUDIES BREAK DOWN: MAGNITUDE, FREQUENCY, SUBJECTS (GENDER IGNORED)

	≥ 61 msec (change from baseline)		≥ 30 ≤ 60 msec (change from baseline)		Baseline[A] ≤ 425 msec & Post ≥ 426 msec	
	Frequency (N)	Subjects (N)	Frequency (N)	Subjects (N)	Frequency (N)	Subjects (N)
QT	6	6[C]	38	28	32	20
QTc	4	4[D]	30	21		

Note: Data summarized from CD ROM (Vol. 3.17)

A= Normal range for absolute QT varies from 330 to 470 msecs (men 400, women 450). Normal Baseline of < 425 msecs has been suggested by the sponsor (vol. 3.1, p. 1.032).
B= According to the European Agency for the Evaluation of Medicinal Products (CPMP), QTc of <430 for males and <450 for females is considered normal and > 450 for males and > 470 for females is considered prolonged (change of 20 msecs). Sponsor suggested values: 440 for males and 460 for females. (vol. 3.1, p. 1.032)
C= Subjects/Patients: 489B014, 489C011, 489F015, 490F027, 490F028, 525E026
D= Subjects/Patients: 488F022, 489F015, 525L005, 525L007
Note that subject 489F015 has been identified with ≥ 61msecs for both QT and QTc. Therefore the number of subjects with QT/QTc ≥ 61msecs is 9.

OptiMARK 20937: SAFETY: ECG:QT BAZETTS[1]: DOSE 0.1mmol/kg: ALL STUDIES BREAK DOWN: MAGNITUDE, FREQUENCY, SUBJECTS (GENDER IGNORED)		
	Frequency (N)	Subjects (N)
≥ 20 msec change from baseline	77	57
Baseline ≤ 450 msec & Post ≥ 451msec	30	21
Note: Data summarized from CD ROM (Vol. 3.17)		

1= According to the European Agency for the Evaluation of Medicinal Products (CPMP), QTc of <430 for males and <450 for females is considered normal and > 450 for males and > 470 for females is considered prolonged (increase of 20 msecs from respective baselines). Sponsor suggested values: 440 for males and 460 for females. (vol. 3.1, p. 1.032)

The following table summarizes pertinent clinical information on patients/subjects who experienced QT/QTc prolongation ≥ 61msecs for all studies for 0.1mmol/kg dose:

ALL STUDIES: POST DOSE (0.1mmol) QT/QTc PROLONGATION ≥ 61msecs							
Patient #	TIME POINT						COMMENTS[D]
	I[A]	15 min	30 min	1 hr	2 hr	24 hr	
490F028						X	No History of Renal Impairment[F] or cardiac disease. + Hemodynamic[B] (↓ HR) Change. No Metabolic[C] change. + AE (rash). QT increase of 64msecs. No PR change. + QRS prolongation. Normal Sinus Rhythm (NSR) with no significant change from baseline per independent cardiologist.
490F027						X	No case report forms available. QT increase of 76msecs.
488F022						X	QTc increase of 64msecs. No renal or cardiac history. No metabolic changes. No PR or QRS changes. No significant hemodynamic changes. No AE. Normal EKG per independent cardiologist.
525E026						X	QT increase of 80msecs. + Cardiac history. No renal impairment. Hypocalcemia @ 24 hours post. No hemodynamic changes. No AE. No PR or QRS changes. + T wave changes. NSR with nonspecific T wave post dose per independent cardiologist.
525L007						X	QTc increase of 78 msecs. No cardiac history. No AE. No hemodynamic changes. No PR or QRS changes. Unable to comment on metabolic changes due to typographical errors in labs (vol. 3.25, p. 25.232). NSR per independent cardiologist.
525L005						X	QTc increase of 74 msecs. No case report forms.
489F015				X			See table below "Study 489 Post Dose QT/QTc Prolongation".
489B014						X	
489C11					X		
Ref: Appendix 26-CD ROM; Appendix 27-Patient Profiles; Appendix 20, vols. 3.11-3.14-Independent cardiologist report							

A= Immediate post dose

B= Systolic Blood Pressure (SBP) ≥ 15mmHg decrease from baseline, Diastolic Blood Pressure (DBP) ≥ 10mmHg decrease from baseline, Heart Rate (HR) ≥ 20 beats/min decrease from baseline

C= Addresses Calcium (hypocalcemia) or others

D= Includes comments on PR and QRS intervals. When none made, implies that there were no significant changes (i.e. no increase in PR ≥ 201msecs and QRS ≥ 101msecs from normal baseline of PR ≤ 200 and QRS ≤101; does not include high baseline → high post dose)

E= These patients with ≥ 61 msecs QT/QTc were identified in the data from Appendix 26 (CD-ROM) and not in Appendix 27 (Patient Profiles). This is a discrepancy that is concerning. The case report forms are not included.

F= Renal Impairment defined by the sponsor as serum creatinine ≥ 1.5mg/dl for study 538 and 1.5 times upper limit of normal range for study 489.

As mentioned above (adequacy section), studies 489 and 538 are the only two studies in this drug program that incorporate more frequent time points at which ECGs were obtained, and when QT/QTc was measured; thereby making these two studies the "the back bone" upon which the data rests. Bulk of the data was collected only at 24 hours following dosing (for all the other studies). This latter data (at 24 hours) is relatively less meaningful and less informative is addressing the effects of OptiMARK, given its metabolism.

There was no monitoring during dosing in this entire drug program, and the first monitoring occurred at 15 minutes post dosing in studies 489 and 538 only.

Study 489 is the only study in this program, which addresses dose-ranging effects of OptiMARK. Emphasis was therefore placed on these two trials and a separate analyses (due to discrepancy as mentioned in the background information section on page 1) using appendix 26- CD ROM containing patient data base, was carried out by the reviewer. All QT/QTc changes ≥ 30msecs were flagged and the following observations were noted for these two studies:

STUDY 538: POST DOSE (0.1mmol) QT/QTc CHANGE ± ≥ 30msecs

Patient #	TIME POINT						COMMENTS[D]
	I[A]	15 min	30 min	1 hr	2 hr	24 hr	
A003						X	+ History of Renal Impairment[F]. + Hemodynamic[B] (↓ SBP) Change. No Metabolic[C] change or reported Adverse Events (AE)
A005			X	X			+ History of Renal Impairment. No Metabolic change or reported Adverse Events (AE). + Associated significant T wave changes @ 1 hour and 24-hour post. Considered to be substantial by the independent cardiologist reflecting "silent ischemia" (vol. 3.1, p. 1.140).
B001[E]		X	X	X	X		No case report forms available.
C003[E]			X				
C006[E]						X	
C009[E]					X		
D005[E]				X			
D009[E]				X			
D010		X			X		+ History of Renal Impairment. ↓ SBP and ↓ DBP + Prolonged PR. No Metabolic change or reported Adverse Events (AE)
E002				X			+ History of Renal Impairment. ↓ SBP and ↓ DBP. No Metabolic change or reported Adverse Events (AE)
E004				X		X	+ Prolonged PR. + Prolonged QRS. No significant hemodynamic, metabolic or AE reported
E009			X				+ History of Renal Impairment. ↓ DBP. No Metabolic change or reported Adverse Events (AE)
G003					X		↓ DBP. + Prolonged QRS. + AE (body, CNS, Special Senses)
G006	X					X	+ AE (headache). No other associations except T wave changes @ 24 hours post.
G008						X	+ AE (SOB). + History of Renal Impairment. ↓ DBP. ↓ SBP. ↓ HR. + PVCs at 1 hr. and 2 hrs. post.

Ref: Appendix 26-CD ROM; Appendix 27-Patient Profiles; Vol. 3.1, p. 1.134 (T/U waves)

A= Immediate post dose

B= Systolic Blood Pressure (SBP) ≥ 15mmHg decrease from baseline, Diastolic Blood Pressure (DBP) ≥ 10mmHg decrease from baseline, Heart Rate (HR) ≥ 20 beats/min decrease from baseline

C= Addresses Calcium (hypocalcemia) or others

D= Includes comments on PR, QRS and T intervals. When none made, implies that there were no significant changes (i.e. no increase in PR ≥ 201msecs and QRS ≥ 101msecs from normal baseline of PR ≤ 200 and QRS ≤101; does not include high baseline → high post dose).
E= These patients with ≥ 30msecs QT/QTc change were identified in the data from Appendix 26 (CD-ROM) and not in Appendix 27 (Patient Profiles). This is a discrepancy that is concerning. The case report forms are not included.
F= Renal Impairment defined by the sponsor as serum creatinine ≥ 1.5mg/dl for study 538.

Note: The following inferences may be drawn from the table above for study 538:

- 15/54 subjects experienced ≥ 30msec change (±) in QT/QTc interval in study # 538. --
- 9 of these 15 subjects (identified by the shaded areas- B001, C003, C006, D005, D010, E009, G003, G006 and G008) had QT/QTc prolongation of ≥ 30 and ≤ 60 msec (0.1mmol/kg dose at all time points).
- There were no subjects in this study (# 538) who had QT/QTc prolongation of ≥ 61 msecs.
- 5 of these 15 subjects experienced QT/QTc change at more than one time point in study # 538.
- Case report forms (CRFs) for 6 of these 15 subjects are not available to make further comments.
- 6 of the 9 subjects (in whom the respective CRFs are available) had renal insufficiency associated in study # 538 along with the QT/QTc change.
- 6 of the 9 subjects (in whom the respective CRFs are available) had associated hemodynamic changes along with the QT/QTc change in study # 538.
- 3 of the 9 subjects (in whom the respective CRFs are available) had associated Adverse Events (of which one patient experienced SOB) along with the QT/QTc change in study # 538.
- 3 of the 9 subjects (in whom the respective CRFs are available) had associated other EKG changes (PR and or QRS prolongation) along with the QT/QTc change in study # 538.
- 2 of the 9 subjects (in whom the respective CRFs are available) had associated T wave abnormalities along with the QT/QTc change in study # 538, of which the changes on patient A005 were considered substantial and representing "silent ischemia" by the independent cardiologist (vol. 3.1, p. 1.140). One patient (G008) was identified as having T wave changes (amongst others) in the earlier submission (vol. 2.39, p.8.2663).
- One patient (G008) had associated PVCs (identified in the current and the earlier submission).
- Additional Comments:
  In the absence of appropriate data (baseline QT/QTc "variability" and post drug "variability"), comments on an unidirectional (minus 30msecs) or bi-directional (± ≥ 30msecs) changes in QT/QTc cannot be made that would adequately address the concerns if OptiMARK caused any variability (or dispersion) in QT/QTc. However, it is worth noting that this pooled data of QT/QTc changes of ≥ ± 30msecs were associated with several clinically significant concerns as indicated in the table above.

STUDY 489: POST DOSE (0.1 mmol/kg) QT/QTc PROLONGATION								
Patient #		TIME POINT						COMMENTS[D]
		I[A]	15 min	30 min	1 hr	2 hr	24 hr	
A008	≥ 30 ≤ 60				X	X		+ History of Renal Impairment[F] & Cardiac disease + Hemodynamic[B] (↓ DBP, ↓ HR). No Metabolic[C] change. + AE (Tachycardia). No PR or QRS changes.
B017					X	X		+ History of Renal Impairment. + Metabolic change (hypocalcemia). +AE (site reaction, warm feeling). ↓ HR. No PR or QRS changes
D019					X		X	No significant history. No AE. ↓ DBP. No PR or QRS changes.
E003							X	No significant history. No AE. ↓ DBP. + QRS prolongation. No PR changes.
E021				X	X	X	X	+ History of Renal Impairment. No AE. No metabolic changes. No hemodynamic changes. No PR or QRS changes.
J013[E]				X	X			No Case Report Form
B014	≥ 61						X	No cardiac or renal history. + AE (musculoskeletal). No metabolic changes. No PR or QRS changes. ↓ DBP (@ 24 hrs). ↓ HR (@ 24 hrs). QT increase of 92 msecs. Sinus bradycardia with intraventricular conduction defect and marked sinus bradycardia @ 24 hrs per independent cardiologist.
C011						X		No renal or cardiac history. + hypocalcemia @ 48 hours. No hemodyamic changes. No PR or QRS changes. QT increase of 80 msecs. + AE (flu like, taste change). NSR with non-specific ST-T wave changes @ 24 hours per independent cardiologist.
F015					X			No cardiac or renal history. No metabolic changes. No hemodynamic changes. No PR or QRS changes. + AE (headache, nausea). QT increase of 84 msecs and QTc of 71msecs. NSR with no significant change per independent cardiologist.
Ref: Append. 26-CD ROM; Append. 27-Patient Profiles; Append. 20, vols. 3.11-3.14-Independent cardiologist report; Vol. 3.1, p. 1.134 (T/U waves)								

A= Immediate post dose

B= Systolic Blood Pressure (SBP) ≥ 15mmHg decrease from baseline, Diastolic Blood Pressure (DBP) ≥ 10mmHg decrease from baseline, Heart Rate (HR) ≥ 20 beats/min decrease from baseline

C= Addresses Calcium (hypocalcemia) or others

D= Includes comments on PR, QRS and T intervals. When none made, implies that there were no significant changes (i.e. no increase in PR ≥ 201msecs and QRS ≥ 101msecs from normal baseline of PR ≤ 200 and QRS ≤101; does not include high baseline → high post dose).

E= This patient with ≥ 30msecs QT/QTc was identified in the data from Appendix 26 (CD-ROM) and not in Appendix 27 (Patient Profiles). This is a discrepancy that is concerning. The case report form is not included.

F= Renal Impairment defined by the sponsor as serum creatinine greater than 1.5 times the upper limit of normal range (normal range not provided) for study 489.

Note: The following inferences may be drawn from the table above for study 489:

- A total of 121 subjects were exposed to OptiMARK of which 40 received 0.1mmol/kg dose in study 489.
- 9 of the 40 (0.1mmol/kg dose group) experienced QT/QTc prolongation ≥ 30msecs of which 3 had QT/QTc prolongation ≥ 61 msecs in study 489.
- 5/9 had QT/QTc prolongation at more than one time point in study 489.
- 1/9 had associated other ECG changes (PR and or QRS) in addition to QT/QTc prolongation in study 489.

- Case report forms are available for 8 subjects.
- 3 of these 8 (in whom the case report form is available) had associated renal insufficiency and one with cardiac disease in study 489.
- 2 of these 8 (in whom the case report form is available) had associated hypocalcemia in study 489.
- 5/8 (in whom the case report form is available) had associated significant hemodynamic changes in study 489.
- 5/8 (in whom the case report form is available) experienced AEs of which one experienced tachycardia in study 489.
- Patient F015 can be identified as having experienced bi-directional (i.e. increase and decrease) QT/QTc changes
- Additional Comments:
  There were 15 patients in study 489 who experienced a QT/QTc change of ≥ ± 30msecs (B002, B009, C007, D024, D027, E007, F004, F015, F021, H002, H012, J009, J013, J017 and K003). Case report forms are available for only two of these patients (E007 and F015). There were no concerns or comments by the independent cardiologist except on patient F015 (see table above). Patient E007 experienced AE (headache and dizziness), ↓ in SBP in addition to the QT/QTc change.
  In the absence of appropriate data (baseline QT/QTc "variability" and post drug "variability"), comments on an unidirectional (minus 30msecs) or bi-directional (± ≥ 30msecs) changes in QT/QTc cannot be made that would adequately address the concerns if OptiMARK caused any variability (or dispersion) in QT/QTc. Whether there is cause for similar concerns on the associations as noted in study 538 (see above) is undeterminable for this study 489 in the absence of the respective case report forms.

II.B EFFECTS OF OptiMARK ON ATRIAL DEPOLARIZATION AND ATRIO-VENTRICULAR CONDUCTION → PR INTERVAL

Atrial depolarization and atrio-ventricular conduction is customarily measured by the PR interval. The table on page 3 of attachment 1 gives information on the studies and the time points of data collection. Vol. 3.1 (pp. 1.032, 1.036) contains the normal acceptable values upon which the data has been re-analyzed by the sponsor. Sponsor's summary table (vol. 3.1, p. 1.105) identifies ~ 33 PR abnormalities for all studies at all time points for 0.1mmol/kg dose. Additional data is also presented in the summary table in the summary section III below.

The findings of the effects of OptiMARK on PR interval was derived from the CD-ROM for all post dose PR prolongation of ≥ 201msecs (baseline of ≤ 200 or ≥ 120 ≤ 200) for all studies for the proposed labeling dose of 0.1mmol/kg at all time points and the following observations were made:

- There were 15 PR prolongations (≥ 201msecs) identified in 11 subjects/patients.
- Two of these patients/subjects (538D010, 538E004) had associated QT/QTc prolongation of ≥ 30msecs.
- Three of these patients/subjects (488F030, 489D021, and 538E004) had associated QRS prolongation of ≥ 101msecs.

II.C EFFECTS OF OptiMARK ON VENTRICULAR DEPOLARIZATION → QRS INTERVAL

Ventricular depolarization is customarily measured by the QRS interval. QRS represents spread of impulse through the ventricles (activation or depolarization) and any

prolongation implies abnormal or delayed intraventricular conduction and usually means block of one of the bundle branches or a ventricular arrhythmia. Morphological changes and characteristics of the QRS complex are equally important and such comments cannot be made, as the actual tracings have not been submitted. The table on page 3 of attachment 1 gives information on the studies and the time points of data collection. Vol. 3.1 (pp. 1.032, 1.036) contains the normal acceptable values upon which the data has been re-analyzed by the sponsor. Sponsor's summary table (vol. 3.1, p. 1.105) identifies ~ 115 QRS abnormalities for all studies at all time points for 0.1mmol/kg dose. Additional data is also presented in the summary table in the summary section III below. The findings of the effects of OptiMARK on QRS interval were derived from the CD-ROM for all post dose QRS prolongation of ≥ 101msecs (baseline of ≤ 100 or ≥ 50 ≤ 100) for all studies for the proposed labeling dose of 0.1mmol/kg at all time points and the following observations were made:

- There were 50 QRS prolongations (≥ 101msecs) identified in 30 subjects/patients.
- Three of these patients/subjects (488F030, 489D021, and 538E004) had associated PR prolongation of ≥ 201msecs.
- One of these patients/subjects (538G003) had associated QT/QTc prolongation of ≥ 30msecs.
- One of these patients/subjects (525E024) had associated U waves at 24 hours post dose

II.D EFFECTS OF OptiMARK ON VENTRICULAR REPORALIZATION → T/U WAVE ABNORMALITIES

T wave represents ventricular repolarization and U wave probably represents repolarization of the papillary muscles and or the Purkinje system. In the cardiac cycle, the U wave coincides with the phase of supernormal excitability during ventricular recovery (at about the same time that most ventricular extrasystoles occur). T wave and U wave abnormalities are generally considered nonspecific, but when abnormal and in particular when associated with other ECG abnormalities (e.g. ST segment or QT changes), clearly represent altered repolarization and vulnerability for potential ventricular arrhythmias. The morphological changes (direction, shape and height) are most important when one makes an assessment of T/U abnormalities. The actual tracings have not been provided and comments are therefore restricted.

According to the sponsor (vol. 3.1, p. 1.134), 228 patients/subjects were noted to have abnormal T/U waves, of which 8 patients/subjects had shifts from normal to abnormal. The following observations were noted:

OptiMARK: NDA 20937: SAFETY: EKG: POST DOSE ABNORMAL T or U: ALL STUDIES: ALL DOSES			
Patient/ Subject	**Dose (mmol/kg)**	**Time Point**	**Other Comments[D]**
525E024	0.1	U @ 24 hrs.	No QT/QTc changes. + QRS prolongation. No AE. No hemodynamic changes[B]. No metabolic changes[C].
525E026		T @ 24 hrs.	Associated + QT/QTc prolongation. No other changes.
538A005		T @ 1hr and 24 hrs.	Associated + QT/QTc prolongation: Substantial change probably representing silent ischemia per independent cardiologist. See section IA, table 538 above.
538G006		T @ 24hrs.	Associated + QT/QTc prolongation. See section IA, table 538 above.
489D004	0.3	T @ immediately post, 15 min., 1 hr., 2 hr.	+ History of HTN. No other cardiac or renal history. No AE. No PR/QRS/QT changes. No hemodynamic changes. Sinus bradycardia with nonspecific T wave changes per independent cardiologist. No metabolic changes.
489H004		T @ 1 hr. and 2 hrs.	No renal or cardiac history. + AE (hand swelling). ↓ SBP 1 hr. post. ↑QT 2 hr. post (40msecs). Nonspecific changes per independent cardiologist. No metabolic changes. No PR/QRS changes.
489J011		T @ 2 hrs.	+ Cardiac history. No renal insufficiency. No metabolic changes. + AE (headaches; hyperesthesia). ↓ DBP and SBP. No PR/QRS/QT changes.
489D018	0.5	U @ 15min, 2 hrs. and 24 hrs. T @ 15 min, 24 hrs.	No cardiac or renal history. No AE. No metabolic changes. No PR/QRS changes. + QT prolongation (35msecs) @ 24 hrs. post. ↑ in U compared to baseline considered to be nonspecific per independent cardiologist.
Ref: Vol. 3.1, p. 1.134; Sections IIA, IIB, IIC of review; Volumes related to respective patient case report forms			

B= Systolic Blood Pressure (SBP) ≥ 15mmHg decrease from baseline, Diastolic Blood Pressure (DBP) ≥ 10mmHg decrease from baseline, Heart Rate (HR) ≥ 20 beats/min decrease from baseline

C= Addresses Calcium (hypocalcemia) or others

D= Includes comments on PR, QRS and T intervals. When none made, implies that there were no significant changes (i.e. no increase in PR ≥ 201msecs and QRS ≥ 101msecs from normal baseline of PR ≤ 200 and QRS ≤101; does not include high baseline → high post dose). Also when none made, implies that were no significant hemodynamic and or metabolic changes.

II.E COMBINED EFFECTS ON PR, QRS, QT/QTc AND T/U:

Using the same criteria (to flag PR, QRS and QT/QTc prolongation) as mentioned above (IIA, IIB and IIC), the following patients/subjects were identified as having more than one prolongation (either PR and or QRS and or QT/QTc and or T/U wave abnormalities) for all studies and for a dose of 0.1mmol/kg):

SAFETY: OptiMARK: NDA 20937: ALL STUDIES: 0.1mmol/kg EKG POST DOSE CHANGES IN MORE THAN ONE MEASURED PARAMETER				
Subject/Patient	PR (≥ 201msecs)	QRS (≥101msecs)	QT/QTc (≥30msecs)	T/U Abnormality
538D010	X		X	
538E004	X	X	X	
538G003		X	X	
488F030	X	X		
489D021	X	X		
525E024		X		U
525E026			X	T
538A005			X	T
538G006			X	T
Ref: Sections IIA, IIB, IIC of review; Vol. 3.1, p.1.134				

IIF. OVERALL EFFECT ON THE RHYTHM:

There were several patients in this drug program who experienced a change in the cardiac rhythm (arrhythmias) following exposure to OptiMARK. Reference is made to the table in attachment 1, page 6, which summarizes some of these changes that include sinus tachycardia, sinus bradycardia, PACs, PVCs, etc. There was the occurrence of poor R wave progression and bundle branch block along with some of these changes. It is worrisome that the present submission does not include some patients that were identified as having PVCs in the earlier submission and the sponsor has not addressed these. The corresponding case report forms are not submitted. Patient 538G008 has been discussed in section IIA (table 538) above. It is important to recognize that this list may not be complete. It is the reviewer's intentions to present this information for purposes of making the association. Cursory review of the earlier submission identified the following patients with PVCs:

SAFETY: OptiMARK: NDA: 20937: EKG: ABNORMALITIES (PVCs): ALL STUDIES		
Patient/Subject	NDA Reference	Comments
538G008	Vol. 2.39, p. 8.2663	PVCs noted @ 1 hr and 2 hrs; T waves @ 15 min.; QT prolongation @ 24 hrs. Also associated significant hemodynamic changes
486A028	Vol. 2.127, p. 20.4041	Dose of 0.2mmol/kg; no case report forms
490G003	Vol. 2.76, p. 14.3244	No case report forms
525F011	Vol. 2.66, p. 13.3042	No case report forms

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III. SUMMARY OF FINDINGS:

The preclinical data was not sufficient to fully characterize the cardiovascular/electrophysiologic effects associated with OptiMARK.

It is evident that the data on which the effects of OptiMARK on the heart can be assessed rests on a limited base thereby making the extrapolation less robust. There were no deaths or serious adverse events attributable directly to the cardiac effects of OptiMARK. Although direct comparison between Magnevist (approved comparator) and placebo was not made in this review (these were addressed in the earlier NDA review), it is suffice to say their safety profiles are similar.

It is lucid that OptiMARK is associated with post dose changes affecting several electrophysiological cardiac events and parameters (PR, QRS, QT, and T/U), alone or sometimes in combination (see table in section IIE above) and at times at more than one time point for the same parameter (section IIA). The frequency and magnitude of these changes (as discussed above in section IIA, IIB, IIC) are additionally of significant clinical relevance, especially for the fact that these stem from a rather "narrow" database.

The table below summarizes the changes in frequency and magnitude of all measured parameters for all studies and doses at all time points.

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SAFETY: OptiMARK: NDA 20937: EKG POST DOSE PR, QRS, QT CHANGES ALL STUDIES: ALL DOSES: ALL TIME POINTS				
	Dose in mmol/kg			
	0.1	0.2	0.3	0.5
Exposed Subjects (N) for all time points	710	121	47	39
All Reads (N) from Immediate to 24 hrs post dose				
PR	686	107	47	38
QRS	690	110	47	38
QT	387	not measured by sponsor	42	38
QTc				
QT Bazett				
All Abnormalities (N) from Immediate to 24 hrs post dose				
PR >200msecs	46	2	11	27
QRS > 100msecs	205	6	47	25
QT 30-60msecs increase from baseline	38	not measured by sponsor	9	12
QT >60msecs increase from baseline	6		1	0
QTc 30-60msecs increase from baseline	30		4	8
QTc >60msecs increase from baseline	4		0	1
QT Bazett 30-60msecs increase from baseline	25		4	7
QT Bazett >60msecs increase from baseline	4		0	1
All Reads (N) from Immediate to 2 hrs post dose				
PR	101	not measured by sponsor	42	38
QRS				
QT				
QTc				
QT Bazett				
All Abnormalities (N) from Immediate to 2 hrs post dose				
PR >200msecs	20	not measured by sponsor	10	25
QRS > 100msecs	113		37	21
QT 30-60msecs increase from baseline	20		6	10
QT >60msecs increase from baseline	2		1	0
QTc 30-60msecs increase from baseline	14		4	5
QTc >60msecs increase from baseline	1		0	1
QT Bazett 30-60msecs increase from baseline	10		4	5
QT Bazett >60msecs increase from baseline	2		0	1
Ref: Vol. 3.1, pp. 1.114-1.131 Note: These numbers may not be exact				

The frequency and magnitude of QT/QTc prolongations (see table above) observed at 24 hours post dose (out of 387 reads) were fewer than that seen at earlier time points (out of 101 reads). This demonstrates the need for more frequent reads at earlier time points. It is known well that the risk of malignant arrhythmia seems to increase with increasing QT interval, but there is no well-established threshold duration, below which a prolonged QT interval is known to be harmless. Failure to observe malignant arrhythmias in small sized trials (such as these with a narrow database) does not fully eliminate such a possibility, because, the actual incidence of malignant arrhythmias, even in association with drugs most known to induce them, is relatively low. There were no other explanations provided in the available data for these prolongations. There were cases with associated PVCs (see

below). Appropriate mentioning of these changes in the proposed labeling is therefore warranted.

As mentioned above (section IIF), there were patients/subjects who experienced rhythm changes amongst which there were a few who had PVCs and one such patient (538G008) had additional changes in QT, QRS, T and blood pressure. The case report forms for the other patients with PVCs were not submitted. Nonetheless, it is prudent to note this observation at this time so that it can be factually mentioned in the label.

Given the "narrowness" of the database, it is again rather speculative to attribute OptiMARK to any particular event, but there are some associations that are worth mentioning. These include some of the associated asymptomatic hemodynamic changes (blood pressure and heart rate; see section IIA above; see page 31 of initial NDA review of Japanese study), metabolic changes (hypocalcemia, see section IIA above; see page 32 of initial NDA review of Japanese study) and the occurrence of ECG changes in patients with a history of renal insufficiency (see section IIA above; see page 51 of initial NDA review of serious adverse event on patient 543-A-003 in study 543). There is some degree of correlation between the timing of electrical abnormalities, drug metabolism and the hemodynamic changes that were observed (see tables in section IIA above; see initial review of study 1177, pp. 23-33). The early occurrence (from immediate to 2 hour post dose) and the persistence of some of the post dose changes can be attributable to the pharmacology and metabolism of OptiMARK, while others cannot (e.g., QT prolongation seen at 24 hours post dosing in patients without renal insufficiency). The presented data was not sufficient to make any attribution or comments or judgement on QT/QTc "variability/dispersion" for the two studies (538 and 489) that were analyzed in depth. Additionally, the lack of such information (positive or negative) at this time on variability/dispersion alone probably does not significantly nullify or augment the impact of the other findings and associations that can be attributable to OptiMARK. Attribution of these latter findings and associations to other causes such as other drug effects/concomitant medication effect, significant past medical history (except renal insufficiency), etc. has not been studied in this program.

Whether the narrowness of the database has any impact in the assessment of dose related ECG changes with OptiMARK, is difficult to judge. Nonetheless, it is important to note from the table above (summary section III above and combined table in section IIA) that there is a suggestion of greater frequency of QT/QTc abnormalities (with respect to the number of exposures) for the higher dose groups when compared to the 0.1mmol/kg dose. Also (table section IID), T/U abnormalities were seen at greater frequency (with respect to the number of exposures).

IV. CONCLUSION

When comparison is made between the total number of patients/subjects exposed (710 for proposed labeling dose of 0.1mmol/kg), to the number of patients/subjects with tracings/records (101) that are relatively informative (as it relates to the metabolism at

frequent time points), the looseness and the narrowness of this data is obvious. Modification by reinforcement of this data is a possibility (via additional preclinical and clinical studies), but probably not warranted at this time. However, appropriate reflection of the narrowness on which this safety database rests should be made in the label. Attachment 2 (an addendum to the review) provides an overview on the issue of gadolinium agents and QTc prolongation in general- summarizing previous experience with the approved agents (Magnevist, Prohance and Omniscan) and their recent AE Search Report; the present concerns based on literature review of calcium channel blockade and other cardiac/toxicity effects; references; and suggestions for the future. Besides the OptiMARK data, Attachment 2 provides additional important information that may be useful in the reinforcement of appropriate recommendations and regulatory decision making.

Despite this narrowness, there were ECG changes (post dose) affecting several parameters (alone or in combination) and at various time points (sometimes at more than one time point) with no definite pattern or consistency. No definite statistical correlation can be made at this time between the noted associations (renal failure, hypocalcemia, hemodynamic changes, etc.) and the electrocardiographic abnormalities largely due to the limitations in sample size. A definitive trend or pattern in any of these abnormalities was not noted, and neither did the data reveal a linear or non-linear effect on QT/QTc by OptiMARK. Whether a larger database may add more light is speculative. Likewise, the data does not portray OptiMARK to be a thoroughly benign drug with respect to the heart. OptiMARK may be considered reasonably "safe" from the perspective that there were no deaths or serious adverse events directly attributable to the cardiovascular effects; but one cannot ignore the data and rule out the possibility that such a potential to trigger a deadly ventricular arrhythmia does not exist. The probability and the likelihood that OptiMARK might cause a fatal arrhythmia is unknown. Even drugs known to cause life-threatening arrhythmias have not shown a consistent trend or pattern. One common potentially attributable known denominator (the others have not been studied or identified) to these post dose abnormalities was the introduction of OptiMARK into the patients/subjects. The database does not strongly point to high-risk patient (underlying/preexisting conditions) groups either, to make any other attribution. Analyses to determine its statistical significance has not been performed.

The data, therefore necessitates the incorporation of these findings (factually) in the proposed labeling which would thereby provide an opportunity for the consumer/clinician (of OptiMARK) to be cognizant of these occurrences, there by facilitating its appropriate use. It is important to recognize the fact that fatal arrhythmias may or may not occur even with the appropriate labeling; but such incorporation would be a reasonably complete representation of the effects of OptiMARK on the heart. Of course, until better data from appropriate additional pre-clinical and clinical trials can reveal new information, deviance from citing these findings in the label is not recommended.

V. SUGGESTED LABELING RECOMMENDATIONS:

VI. RECOMMENDATION:

Approval with label changes.

/S/ 11/4/99
Ramesh Raman, MD
Medical Officer

/S/
Sally Loewke, MD
Medical Team Leader

/S/ 11/29/99
Patricia Y Love, MD
Division Director, HFD 160

cc:
HFD-160: IND Archive
HFD-160: Division File
HFD-160: Division Team Leader
HFD-160: Review Team: Raman, Moore, Loewke, Lee, Davi, Melograna, Place

ATTACHMENT 1 TO ECG SAFETY REPORT: NDA 20937
(Ref: Letter Date: June 7, 1999)

ELECTROCARDIOGRAM:

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- The following are the primary concerns regarding EKGs:

1. The Sponsor chose the following parameters to define "extreme" values across the trials in this clinical program. These were:

PR Interval	<60 msec	>240 msec
QRS Interval	<40 msec	>160 msec
QT Interval	<200 msec	>500 msec

These "Sponsor chosen" parameters are too liberal (wide) and unacceptable. Standard references in cardiology (Henry Marriott's Practical EKG) and internal medicine text books (Cecil's 20th edition) consider the following ranges as normal or upper limits of normal:

1. PR Interval = 0.12 secs (120msec) to 0.20 secs (200msec) with 240 msec being the maximum upper limit of normal.
2. QRS Interval = 0.05 to 0.10 secs (50 to 100 msec) with 0.11 secs (110 msec) being considered the maximum upper limit of normal
3. QT Interval = rate dependent; 0.36 secs (360 msec) to 0.39 secs (390 msec) at an average rate of ~ 75 beats per minute

2. According to the Sponsor, these EKGs were read mostly by the principal site investigators who were all/mostly radiologists.
2. It is not clear whether these were automated or manual readings. It is very important to know this specially when interpreting QT intervals when hypokalemia or hypocalcemia (known to occur with OptiMARK™- see phase 1 studies and precautions) co-exists.
4. Although a total of 1684 subjects/patients were enrolled in this clinical development program and a total of 1309 subjects/patients were dosed with OptiMARK™ and 329 patients were dosed with Magnevist®, the total number of patients who had complete meaningful EKG records were significantly fewer than what was proposed or planned. Several of these trials did not have EKG (including those in which it was proposed in the study protocol) as safety monitoring parameter (see table below). **In particular, in study 433 which was the first-in-human study (subjects received doses as high as 0.7 mmol/kg), the Sponsor did not perform any EKGs** (study 433, Vol. 2.147, p.26.0265). Additionally, those patients in the phase 2 and phase 3 studies who were on many medications and medically sick were potential targets for cardiac arrhythmias (pre-disposition). The timing and frequency in these cases were also inadequate. In those studies in which EKGs were obtained, the records were incomplete (no QT or QTc readings, etc) to a significant degree. Readings in some trials included only the interpretation as "normal" or "abnormal" without providing the intervals/values. Of the 1684 patients/subjects enrolled in this study, ~680 (40.38 %) patients had values that can be potentially interpretable (if the tracings are still available). But then again, the data was presented as means and SDs and changes were accordingly reflected without the baselines. The actual tracings have not been

provided either. Then the matter of who read and interpreted these records (man or machine?; radiologist or internist or cardiologist?) remains and is unsettled at this time.

5. The best utilizable data (in terms of adequacy and timing) could potentially stem only from the phase 1 studies (489 and 538, N=163 records); because the others were inadequate in terms of frequency and completeness. Specifically, in the phase 3 studies, EKGs were obtained only at a 24-hour post-dosing interval after a pre-dose baseline. Obtaining a single 24-hour post reading (after the baseline) has no clinically meaningful significance based on the pharmacokinetics of gadolinium. The importance of this issue (correlation of the pharmacokinetics with any adverse event and its, monitoring) is highlighted in the patient in the Japanese study-phase 1, who developed a significant bradycardia with EKG changes during the 2 to 8 hour post-drug window that was also associated with hypocalcemia. All events normalized after 8 hours (all subjects were normal healthy volunteers).
6. There was no monitoring during the dosing or during imaging (when carried out).

- The table below summarizes these deficiencies:

SAFETY: DEFECIENCIES: ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937				
Study Number	**N (enrolled) =1684**	**Potentially useable* data (N=680)**	**NDA Volume Reference**	**COMMENTS**
Phase 1 – Dose Ranging, Pharmacokinetic Studies				
433	16	0	2.10	Protocol called for EKGs, but none performed - ? violation
489	121	109	2.28	12 incomplete records
538	54	54	2.39	No specific comments (see general comments)
539	Application does not include this trial (Sponsor chose not to submit- Pediatric trial-Ongoing)			
543	8	8	2.43	No specific comments (see general comments)
Phase 2 – Pseudo Cross Over Dose Ranging Studies				
464	83	0	2.147	No planned EKG in any of these studies
465	89	0		
466	36	0		
467	86	0		
468	5	0	2.136	Although EKGs were performed, no intervals or relevant information is provided other than an overall interpretation
469	72	0	2.142	
Phase 3 – Open-Label Studies				
484	15	0	2.117	Entirely incomplete records where QT intervals were not recorded at all. Of all the parameters, QT interval is probably the most important interval that needs attention in such drug trials
485	39	0		
486	98	0	2.127	
487	122	0		
Phase 3 – Comparative Pivotal Comparative Studies				
488	201	141	2.56	~ 60 of the 201 –mostly lacking QT intervals or other parameters
490	193	96	2.76	~ 97 of the 193 patients had incomplete records as in 488
525	194	125	2.66	~ 69 of the 194 patients had incomplete records as in 488
526	202	147	2.86	~ 55 of the 202 patients had incomplete records as in 488

Note: These numbers are approximates and may or may not reflect the actual numbers; but provides as estimate.
*includes intervals (including QT); deficient in the frequency, timing and parameters.

- 12 lead EKGs were performed at various time points during these trials. These are summarized as shown in the table below:

SAFETY: TIMING OF ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Phase I – Dose Ranging, Pharmacokinetic Studies							
433	None						
489	X	X[1]	X		X		
538	X	X[1]	X		X		
1177	X	X[3]					
543	X	X[2]			X		
Phase 2 – Pseudo Cross Over Dose Ranging Studies							
464	None						
465							
466							
467							
468	X	X[3]					
469	X				X		
Phase 3 – Open-Label Studies							
484	X				X		
485	X				X		
486	X				X		
487	X				X		
Phase 3 – Comparative Pivotal Comparative Studies							
488	X				X		
490	X				X		
525	X				X		
526	X				X		

1= includes immediate post dosing, 15 minutes post dosing, 30 minutes post dosing, 1 hour post dosing, 2 hours post dosing
2= 1 hour post dosing 3= 2 hours post dosing

SUMMARY OF EKG FINDINGS: ALL STUDIES COMBINED:

- The sponsor has provided summary descriptive statistics for ECGS (PR, QRS, HR, QT_c) by dose and treatment for all patients or subjects enrolled in all studies in Tables 9.1.1-1 through 9.5.1-7 (Vol. 2.147) for baseline and 24 hours after the start of injection.
- According to the Sponsor, although these changes reached statistical significance, the overall mean change was small and were not felt to be clinically relevant or thought to represent a cardiac electrophysiological effect.
- Statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: ALL STUDIES COMBINED: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		**Comments**
OptiMARK™	0.1	Statistically significant increase for heart rate Statistically significant decreases for PR and QT
	0.2	No statistically significant increases or decreases
	0.3	No statistically significant increases or decreases
	0.5	No statistically significant increases or decreases
	All doses	Statistically significant increase for heart rate Statistically significant decreases for PR, QRS, and QT
Magnevist®	0.1	Statistically significant increase for heart rate Statistically significant decreases for PR and QT
Placebo		Statistically significant decreases for QT

EKG: BY PHASES AND DOSE:

EKG BY DOSE: Phase 1 Studies

- A total of 225 subjects or patients were enrolled in three Phase 1 studies (Studies 489, 538, and 543) of OptiMARK™. *EKGs were not performed as part of Study 433.*
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes were small and were felt not to be clinically relevant.
- Statistical comparison of ECG parameter differences from baseline by dose and treatment revealed the following findings at 1 hour and 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 1 STUDIES: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		**Comments**
OptiMARK™	0.1	Statistically significant decreases in heart rate 1 hour post-dosing; in PR and QT at 24 hours post-dosing Statistically significant increase in heart rate 24 hours post-dosing
	0.3	Statistically significant decrease in heart rate 1 hour post-dosing; in PR 24 hours post-dosing
	0.5	Statistically significant decreases in heart rate and QT_c 1 hour post-dosing
	All doses	Statistically significant decreases in heart rate and QT_c 1 hour post-dosing; in PR and QT 24 hours post-dosing
Placebo		Statistically significant decrease for heart rate 1 hour post-dosing; for QT 24 hours post-dosing

EKG BY DOSE: Phase 2 Studies

- A total of 938 patients were enrolled in eight Phase 3 Studies (open-label and comparative studies combined).
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes were small and were not felt to be clinically relevant or different between OptiMARK™ and Magnevist®.
- According to the Sponsor, statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 2 STUDIES: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		**Comments**
OptiMARK™	0.1	No statistically significant increase or decrease
Magnevist®	0.1	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG BY DOSE: Phase 3 Studies

All Studies (Open-Label and Pivotal Studies)

- A total of 938 patients were enrolled in eight Phase 3 Studies (open-label and comparative studies combined).
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes are small and are not felt to be clinically relevant or different between OptiMARK™ and Magnevist®.
- Statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 3 STUDIES: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	595	No statistically significant increase or decreased
Magnevist®	0.1	326	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG BY DOSE: Pivotal Studies

- A total of 790 patients were enrolled in the pivotal studies and received either 0.1 mmol/kg OptiMARK™ or 0.1 mmol/kg Magnevist® in the four pivotal Phase 3 studies.
- According to the Sponsor, although a few parameters attained statistically significant differences from baseline the mean ECG changes were very small with no clinically significant difference between OptiMARK™ and Magnevist® treatment groups.
- Statistically significant mean changes from baseline included:

SAFETY: ELECTROCARDIOGRAMS: PIVOTAL STUDIES: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	452	Statistically significant increase for heart rate 24 hours post-dosing
Magnevist®	0.1	326	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG: BY STUDIES

- The table below summarizes some of the EKG findings by study that were significantly different from the baseline EKG:

SAFETY: SIGNIFICANT CHANGES: ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937					
Study Number (N exposed)	Treatment groups	COMMENTS/ABNORMALITIES (N) Significant changes form baseline	(N) Clinically Significant	All Changes	NDA Ref Vol.
Phase 1 – Dose Ranging, Pharmacokinetic Studies					
433	No EKGs performed				
489 (121)	OptiMARK™	18	5 of 18	QT, ST-T changes in 4 patients	2.28
	Placebo	6			
538 (54)	OptiMARK™	3	1 of 3	T wave inversion, QT interval changes, PVCs	2.39
539	Application not submitted by Sponsor				
543 (8)	OptiMARK™	None reported			2.43
Phase 2 – Pseudo Cross Over Dose Ranging Studies					
464	EKGs not performed				
465					
466					
467					
468 (5)	OptiMARK™	Only overall impressions in the interpretation, no intervals No reported abnormalities			2.136
469 (72)	OptiMARK™				2.142
Phase 3 – Open-Label Studies					
484/485 (15+49)	OptiMARK™	No QT or QTc intervals recorded (100%) None reported			2.117
486 (98)		8	0	2/8 received 0.1mmol dose; 6/8 received 0.2 mmol dose. Poor R wave prog, T wave inversion, ST depresiion, PVCs, Sinus bradycarida No QT/QTc measured (100%)	2.127
487 (122)	OptiMARK™	0	0	None reported No QT/QTc measured (100%)	
Phase 3 – Comparative Pivotal Comparative Studies					
488 201	OptiMARK™	2	0	QT prolongation, T wave inversion	2.56
	Magnevist®	0	0	~ 30% without QT intervals or others	
490 193	OptiMARK™	7	0	~51% without QT intervals or others Poor R wave progression, PVCs, Sinus tach, PACs, ST changes, QT prologation	2.76
	Magnevist®	3	0		
525 194	OptiMARK™	7	0	~ 35% without QT intervals or others Sinus tach, SVT, PVCs, BBB, Prolonged QRS, T wave changes, QT prolongation	2.66
	Magnevist®	4	0		
526 202	OptiMARK™	4	0	~27.22% without QT interval or others Abnormal overall	2.86
	Magnevist®	4	0		

- These numbers are approximate and do not reflect the actual numbers. They give an estimate.

The following conclusions can be drawn from the 'deficiency' tables and the 'significant changes' tables above:

a) ~ 56/1063 (5.2%) EKGs were read by the Sponsor as being abnormal (significant change from baseline). This is based on the wide intervals that the Sponsor has chosen (see comments above).

b) Of these, (N) of incomplete/unusable records (those in which either all the stated intervals are not measured or incompletely commented on-the majority of which are those without QT intervals) = ~ 642 (needs to be eliminated).

c) Therefore the useable meaningful number of records is actually 1063 minus 642 = 421.

d) Therefore, standing on the same grounds as the Sponsor, 56/421 = **13%** is the approximate number of patients who had significant change/s in their EKGs compared to the baseline (when the same parameters are used and when all the abnormal readings are counted once in the useable group). Re-analysis of the records (if available and if complete) with the "accepted" range of parameters for the same number of 421 records (if the other EKG tracings are not salvageable or complete) would probably or most likely yield a larger number of abnormal EKGs post drug exposure. This is a serious safety concern, and specific recommendations need to be made to address this deficiency.

e) Silent EKG changes occurring (electrical abnormality without associated clinical signs or symptoms) should be treated with greater caution than when similar silent/asymptomatic changes occur with some of the other parameters (e.g. labs). These electrical changes may be the harbingers for a serious life threatening devastating event, and the window of opportunity to take the necessary actions is usually very small. It calls for specialists' intervention in an emergent manner. Capturing, recognizing and managing these expeditiously is the single most critical step in managing cardiac events. Uncertainties exist whether such an environment was made feasible or available or even existed in this clinical program. Study 433 is a an extreme example of this concern, in which there were no EKGs at all in this first-in-human study in which the maximum dose of 0.7mmol/kg was administered to some of the subjects, who were all healthy male subjects.

f) In retrospect, despite the inadequacies (for: frequency, timing, capturing, completeness, chosen parameters, etc.) in this program (as for as EKG is concerned), there were no deaths related to cardiac events. But there is no way of determining the actual number of electrical abnormalities as and when they occurred (or if they occurred at all) at this time.

- **Overall EKG Impressions:**

1. Although there were no deaths or serious events attributable to cardiac events by OpitMARK™, the capturing and documentation of these events were inadequate (timing, frequency, completeness, interpretation) and inappropriate (parameters too liberal, no QT intervals).
2. Whether such abnormalities occurred (although there were no mortality associated) at all is unknown.
3. Of the captured data, a significant number of records are incomplete.
4. Uncertainties regarding the appropriateness of background of EKG readers exist (including automated v/s manual readings).
5. The observations noted by the Sponsor are meaningless. Presented data is in a form that is largely clinically meaningless.
6. If approved, the case/s described in the Japanese study necessitates appropriate labeling for bradycardia/EKG changes.

END OF ATTACHMENT 1

ATTACHMENT 2 (ADDENDUM)

GADOLINIUM and QTc PROLONGATION

With reference to the concerns/questions that were raised and discussed on November 29, 1999 during the Optimark labeling meeting regarding all gadolinium compounds potentially causing QTc prolongation and or malignant arrhythmias, the following relevant information is provided that addresses this question at this time.

There is a potential cause for concern for the entire class of gadolinium agents stemming primarily from the following information:

a) Association of Optimark and QTc prolongation (as noted from the data of the NDA) and
b) Information from literature (see references; attached) that suggests blockade of cardiac calcium channels by gadolinium compounds.

In order to address this concern, existing information from several sources was reviewed which is summarized below

1. There is no mention of QTc prolongation and or ventricular malignant arrhythmias (including torsades) in the current package inserts (labels) for the three approved gadolinium agents on the market Magnevist (company Berlex), Prohance (company Bracco) and Omniscan (company Nycomed). However, in the adverse reactions section of the label, there is mention of:

- arrhythmia, tachycardia, non-specific ECG changes, angina pectoris, death related to myocardial infarction or other undetermined causes (Magnevist label)
- rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease (Omniscan label)
- prolonged P-R interval, A-V nodal rhythm (Prohance label).

The effects on QTc were not specifically studied at the time of the NDA approval for any of these drugs and such data was probably not collected.

2. Review of recent literature on adverse events of Magnevist (Clinical Safety of Gadopentetate Dimeglumine; Rad., Vol. 196, No. 2, 439-443, Aug. 1995) did not reveal such an association. Additionally, there was no mention of this association for Magnevist in a recent safety update from the sponsor (letter dated May 6, 1999).

3. Additionally, in conjunction with CDER/ORM/DDREII, a post-marketing search for QTc prolongation and or ventricular arrhythmias and or torsades was carried out on 11-29-1999 (Adverse Event Reporting System- AERS) for all these three approved drugs (attached). The search revealed one case of torsade de pointes in a patient who received Prohance. This patient additionally received propulsid (a drug known well to cause QTc prolongation and torsades) and it was felt that propulsid was the contributory agent for the observed event.

In summary, to date, the existing approved agents were not studied during their respective drug developmental stages to specifically address this issue of QTc prolongation and there are no reports of this concern in their post marketing AE portfolios since their approval. Therefore, in order to adequately resolve or substantiate the preclinical (calcium channel blockade) and clinical (association between Optimark and QTc prolongation) concerns, further well designed preclinical and clinical testing is strongly recommended. These clinical trials should be designed to address dose effects, high-risk populations, concomitant medications, associated medical and metabolic (hypocalcemia, hypokalemia, hypomagnesemia, etc.) conditions, etc. In the interim, monitoring for cardiac events on the AE report should vigilantly be carried out on the products already on the market. Additionally, sponsors seeking approval for new gadolinium products should be encouraged to carry out appropriate preclinical and clinical studies, and sponsors should be pursued for a commitment for Phase 4 trials for their approvable products.

REFERENCES

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5. Essentials of Electrocardiography, Ashman and Hull, 1945
6. Principles of Clinical Electrocardiography, Goldschlager & Goldman, 1989, 13th edition
7. A symposium: QTc Interval Prolongation: Is it beneficial or Harmful?; The American Journal of Cardiology, 1993, Vol. 72, No. 6; Joel Morganroth, MD
8. Clinical Safety of Gadopentetate Dimeglumine; Rad., Vol. 196, No. 2, 439-443, Aug. 1995 - Kevin L. Nelson, MD, et al.
9. The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products - The European Agency for the Evaluation of Medicinal Products, CPMP, London, December 1997
10. Development of Drugs that Alter Ventricular Depolarization; Draft comments; July 1999; Drs. Robert Fenichel, MD, PhD; John Koerner, PhD
11. Scientific Rounds, Dr. Lipicky, April 1998
12. Memorandum on QT intervals; April 1998; Victor Raczkowski, MD, MS

END OF ATTACHMENT 2

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACERTICAL DRUG PRODUCTS HFD-160

Team Leader's Comment:

NDA: 20937
NAME: OPTIMARK
APPLICANT: MALLINCKRODT MEDICAL INC.
SUBMITTED: 02 MARCH 1998
REVIEW COMPLETED: 16 NOVEMBER 1998

Optimark is the fourth new drug application (NDA) of a gadolinium contrast agent reviewed for marketing approval. It is intended for enhancement of magnetic resonance imaging (MRI) of the integrity of the blood-brain-barrier (BBB) of the central nervous system (CNS). It is the first gadolinium agent to claim to facilitate visualization of lesions in the liver.

The studies supporting the overall safety of Optimark and the CNS claim were reviewed by Dr. Raman. The studies supporting the hepatic claim were reviewed by Dr. Yaes.

Please refer to the table titled "SAFETY: SIMILAR (CLASS) PRODUCT INFORMATION" on pages 165 and 166 of Dr. Raman's review which provides the physical and chemical characteristics of these agents and the indications, dosage, warnings, and adverse events.

The trials utilized approved devices that had magnet strengths currently used in MRI practice. Study 488, page 107 of this review, noted that 82% of the studies were conducted with 1.5T devices while the other studies utilized 0.5 and 1.0T devices. Study 525, page 137, utilized 1.5T in 78% of the patients.

The CNS studies comprised an enriched population known to have CNS disease or procedures likely to cause an abnormality in the BBB. In studies 488 and 525 (CNS) 40% of the patients were known to have CNS lesions see page 159, " b) Non representative patient selection".

There are a number of problems in the design, conduct and analysis of these trials that the primary reviewer has described for both efficacy and safety. Proof of efficacy was not supported by a standard of truth to validate the findings of the Optimark studies. The sponsor conducted a comparative trial with Magnevist that provided no evidence that Optimark was equivalent to Magnevist. Nevertheless the sponsor demonstrated that Optimark detected BBB abnormalities. Cardiac safety was not adequately evaluated by electrocardiographic studies which were collected 24 hours following the Optimark dose. Dr. Raman's safety concerns and recommendations are listed on pages 217 and 218. Adequate evaluation of the electrocardiographic (EKG) data is the most imperative safety

issue identified. It is fully presented on pages 185 to 192. Most significantly the PR, QRS and QT normal interval ranges were set too wide to identify potential drug induced cardiac effects. It would require the collection of new EKG data to eliminate this deficiency.

The second primary reviewer, Dr.Yaes, concluded that Optimark should not be approved for the liver efficacy claim because there was no standard of truth to validate the Optimark results and the results suggested that there was very little benefit derived from the use of contrast.

The sponsor did demonstrate that Optimark provided an increase in conspicuity of hepatic lesions and served as an anatomic marker of hepatic disease.

Dr. Yaes is in accord with the EKG safety issue identified in the review of the CNS portion of the NDA.

Conclusion:
Optimark may be approved as an anatomic marker of liver disease and to detect intracranial lesions with abnormal vascularity, as a marker of altered blood brain barrier.

The safety of Optimark has not been adequately determined as the EKG data is deficient.

Recommendation:
Approvable when the existing EKG data is reviewed with standard PR, QRT and QT intervals and a Phase 4 committment has been accepted by the sponsor to study additional patients for EKG data within one to two hours post Optimark dose.

/S/

A. Eric Jones M. D.
Clinical Team Leader
10 December 1998

NDA # 20 937 OptiMARK™
IND#

- **Clinical Reviewer: Ramesh Raman, M.D.**

- Sponsor: Mallinckrodt Medical, Incorporated
- Submission Date: March 1998
- Review Completion Date: 12-4-98 ✓
- Primary Review Team:
  Chemistry: Dr. Place
  Microbiology: Dr. Uratani
  Pharmacology/Toxicology: Dr. Melograna
  Statistical: Ms. Davi
  Biopharmaceuticals: Dr. Choi
  Project Manager: Ms. Colangelo and Mr. James Moore
  Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information provided by Sponsor related to Safety (dated 4-28-98, 7-9-98)

CONTENTS

NDA # 20 937 **OptiMARK™ Regulatory Overview**

This section of the regulatory overview encompasses the following:

1. Regulatory history
2. Overview of drug developmental program including background information on the drug, pharmacologic category, proposed indication, proposed dosage, proposed directions for use, proposed contraindications, proposed warnings, proposed precautions, adverse reactions for proposed labeling.
3. Extent of exposure and demographics
4. Similar (class) products information
5. Overview of all studies by phases
6. Material/s reviewed
7. Broad listing of Reviewer's extent of review
8. General comments on the application
9. Final considerations/options on CNS efficacy
10. Final considerations/options on safety
11. Recommendation

REGULATORY HISTORY

[From Vol. 2.1 pp. 1.0029 - "Key Correspondence" section of NDA]

- IND Application [redacted] was submitted by Mallinckrodt, Inc. on 15 January 1993.
- On 14 April 1993, the FDA provided comments and recommendations to the Sponsor for the clinical plan and revisions were made by the Sponsor to the Phase 1, 2, and 3 clinical studies.
- A pre-Phase 2 meeting was held between the Sponsor and the FDA and the Sponsor submitted revised protocols on 17 November 1993.
- The Sponsor presented the Phase 3 clinical plan to the FDA on 05 September 1995 and revisions were made based on comments and concerns conveyed by the Agency. The revisions were submitted on 24 May 1996 as Amendment -068 to the IND. Additional changes were made following a meeting with the FDA on 01 August 1996. One of these included use of equivalence methodology between OptiMARK™ and a 'comaprator'.
- Following submission of the NDA in March 1998, upon request from FDA, the Sponsor provided a table outlining the changes made to the Pivotal Phase 3 studies (for liver and for CNS indications) in May 1998 [document # T43025 of NDA 20 937]. The following table from this document summarizes the dates of changes and amendments to the Pivotal Phase 3 studies:

Version	Study #	IND Serial #	Date of Change	Date of Amendment
.01	488 & 525 – CNS		04/09/96	05/24/96
.01	490 & 526 – Liver		04/22/96	05/24/96
.02	488 & 525 – CNS		09/26/96	11/11/96
.02	490 & 526 – Liver		09/26/96	11/11/96
.03	488 & 525 – CNS		05/30/97	08/12/97
.03	490 & 526 – Liver		05/30/97	08/12/97

- A program for a pediatric indication was developed following the meeting with FDA and is ongoing at the time of NDA submission

- Additional Phase 1 studies to include renal patients, to obtain pharmacokinetic data, and to assess dialyzability of OptiMARK™ were instituted by the Sponsor in response to FDA's recommendations. Specific details about the pharmacokinetic measures were discussed via telephone conference between the Sponsor and FDA on 03 February 1997 and on 27 February 1997.
- The Sponsor met with FDA on 03 December 1997 prior to NDA submission to provide a synopsis of the clinical trials as well as to review data presentation.
- The Sponsor states that OptiMARK™ has not been marketed overseas.

OVERVIEW OF DRUG DEVELOPMENT PROGRAM

- "OptiMARK Injection is intended for use as an extracellular MRI contrast agent. This drug product is an aqueous solution containing the drug substance gadoversetamide (MP-1177), a nonionic gadolinium chelate and the stabilizer versetamide as the monosodium monocalcium salt." [p. 26.0023, Vol. 2.147]

BACKGROUND INFORMATION ON THE DRUG

General:

The "active ingredient" in OptiMARK™ is a complex consisting of gadolinium (+3) and the chelating agent versetamide. Gadolinium is a paramagnetic ion, which enhances the relaxation rates of immediately surrounding water when placed in a magnetic field thereby increasing brightness when T1-weighted magnetic resonance imaging is performed. OptiMARK™ does not cross the intact blood-brain barrier.

Drug: {for full details, please refer to the Chemistry Review by Dr. Place}
Trade Name: OptiMARK™
Generic 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
Empirical Formula: $C_{20}H_{34}N_5O_{10}Gd$

CONTENTS

Description: non-ionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide)

PHARMACOLOGIC CATEGORY

Gadolinium-containing intravenous contrast agent for magnetic resonance imaging

PROPOSED* INDICATION

[*As proposed by the Sponsor; from the Package Insert]

- The **proposed indications** for OptiMARK™ are: [p. 1.0348, Vol. 2.2]

PROPOSED* DOSAGE AND ADMINISTRATION

[*As proposed by the Sponsor; from the Package Insert]

PROPOSED* DIRECTIONS FOR USE

[*As proposed by the Sponsor; from the Package Insert]

PROPOSED* CONTRAINDICATIONS

[*As proposed by the Sponsor; from the Package Insert]

PROPOSED* WARNINGS

[*As proposed by the Sponsor; from the Package Insert]

PROPOSED* PRECAUTIONS (also see "Proposed Warning" above)

[*As proposed by the Sponsor; from the Package Insert]

PEDIATRIC USE

The Sponsor states that pediatric drug development is ongoing at this time and that no safety or pharmaco-kinetic information is available for this age group at this time.

ADVERSE REACTIONS

- During the clinical trials, 1309 patients or subjects were given OptiMARK™ (total of 1663 injections as 354 patients received two doses).
- There were 8 serious adverse events and 1 death (in a patient with end-stage AIDS) reported during the clinical trials.
- "The most commonly noted adverse experiences were headache (8.4%), taste perversion (4.4%), dizziness (3.1%), nausea (3.0%), vasodilatioin (2.3%) and paresthesia (2.1%)" [p. 1.0214, Vol. 2.1]. The Sponsor reported no demographic association with adverse events.

EXPOSURE AND TRIALS

- A total of 1309 patients received OptiMARK™ of which 354 patients had two doses giving a total number of 1663 exposures. In addition, there were 329 patients who received Magnevist® and 46 patients or subjects who were given placebo.
- The total number of studies contributing to this NDA is 19. Of these, there are five Phase 1 studies (including one study conducted in Japan; the Sponsor stated that the safety data for this could not be integrated with those of the four US studies), six Phase 2 studies, and eight Phase 3 studies. Of the eight Phase 3 studies, "Two open-label CNS studies (Study 484 and 485) and two open-label liver studies (Study 486 and 487) were terminated prior to completion of enrollment in order to incorporate the FDA-suggested study design modifications including a comparator group (i.e., Magnevist®) and overall analytical plan to demonstrate equivalence to the approved comparator"[p. 1.0378, Vol. 2.2]. Of the remaining four Phase 3 studies, Studies 488, 525, 490, and 526 "... were similar in design with common clinical safety monitoring (vital signs, physical exams, ECG's, clinical laboratory parameters, injection tolerance and adverse events) and with generally similar inclusion and exclusion criteria." [p. 1.0379, Vol. 2.2]

DEMOGRAPHICS

- There was a total of 1684 patients/subjects enrolled in all studies of which 1309 were given OptiMARK™ (total of 1663 injections as 354 patients received two doses), 329 were given Magnevist®, and 46 received placebo.
- Of the total 1684 patients/subjects, 870 (52%) were men and 814 (48%) were women; 1718 (84.3%) were White, 183 (9%) were Black, 48 (2.4%) were Asian, and 89 (4.4%) were Others.
- In the OptiMARK™ group, 680 (52%) were men and 629 (48%) were women; the average age was 49.4 years [p. 26.0057, Vol. 2.147]. In the Magnevist® group, 165 (50%) were men and 164 (50%) were women; the average age was 51.4 years. In the placebo group, 25 (53%) were men and 21 (47%) were women; the average age was 44.4 years. Additional information is provided in the "Demographic Overview Table".

REGULATORY: DEMOGRAPHIC OVERVIEW: OptiMARK™			
Parameter	OptiMARK™	Magnevist®	Placebo
Total Number (%)	1309 (~78%)	329 (~19%)	46 (~3%)
Mean Age (years)±SD [Range]	49.52 ± 14.95 [12 - 85]	51.4 ± 14.8 [20 - 86]	44.4 ± 13.0 [21 - 73]
Sex: number (%)			
- Male	680 (52%)	165 (50%)	25 (54%)
- Female	629 (48%)	164 (50%)	21 (46%)
Race: number (%)			
- White	1102 (84%)	268 (81%)	41 (89%)
- Black	116 (9%)	35 (11%)	5 (11%)
- Asian	33 (3%)	11 (3%)	0 (0%)
- Others	58 (4%)	15 (5%)	0 (0%)
Mean Height(cm)±SD [Range]	170.3 ± 10.1 [120 - 208]	170.4 ± 10.3 [140 - 196]	171.9 ± 8.9 [156 - 190]
Mean Weight(kg)±SD [Range]	75.35 ± 16.28 [38 - 145]	76.6 ± 17.3 [42 - 141]	81.4 ± 19.6 [52 - 153]
Mean BSA (m^2) ±SD [Range]	1.88 ± 0.23 [1.22 - 2.68]	1.90 ± 0.3 [1.4 - 2.7]	2.0 ± 0.2 [1.5 - 2.7]

[Data from pp. 26.0058 - 26.0059, Vol. 2.147]

SIMILAR (CLASS) PRODUCTS INFORMATION

See safety overview section.

OVERVIEW OF STUDIES

OVERVIEW OF PHASE 1 STUDIES:

- The Sponsor conducted four Phase 1 clinical trials in the USA in a total of 245 volunteers and patients with doses ranging from 0.1 to 0.7mmol/kg.
  1. Study # 433 was the first-in-human study and was intended to provide pharmacokinetic and safety data in 20 healthy male volunteers at doses of 0.1, 0.3, 0.5, and 0.7mmol/kg OptiMARK™ compared to placebo.
  2. Study # 489 was proposed to assess gadolinium elimination and safety in 163 patients with liver or central nervous system disease who did or did not have co-existing renal impairment. The doses used were 0.1, 0.3, or 0.5 mmol/kg OptiMARK™ or placebo and observation was carried out over 7days.
  3. Study # 538 involved a dose of 0.1mmol/kg OptiMARK™ given to 54 healthy volunteers and patients with hepatic or central nervous system disease.
  4. Study # 543 included 8 adult hemodialysis patients with end-stage renal disease who received a dose of 0.1mmol/kg OptiMARK™ to assess dialysis clearance of the drug.
- One Phase 1 pharmacokinetic study was performed on 20 healthy male volunteers in Japan (the Sponsor stated that the safety data for this could not be integrated with those of the four US studies, but has been submitted for safety review).

- The table below projects an overview of the Phase 1 studies.

OVERVIEW: PHASE 1 STUDIES: OptiMARK™ : NDA # 20937					
Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed
1 03/01/93 04/30/93	433 1101-01	"Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal, Healthy Male Volunteers"	Ascending dose PK study Placebo-controlled	Safety, Tolerance, First-in-human study (No Imaging)	Normal Adult Volunteers N= 16 + 4
1 06/04/96 08/12/97	489 1177-95-04.03	"A Study to Evaluate the Pharmacology of OptiMARK™ (Gadoversetamide Injection) in Patients with Central Nervous System or Liver Pathology"	Double-blind, Single dose, Randomized, Placebo-controlled, Parallel group, Multi-center	Dose related pharm. effects, Safety, Tolerance (No Imaging)	>2 years, Liver/CNS pathology ± renal impairment N=163
1 06/02/97 11/15/97	538 1177-96-08.01	"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"	Open-label, Single-dose, Multi-center	PK, Elimination, Metabolites, Safety, Tolerance (No Imaging)	Normal Adults, Adults with CNS/Liver pathology ± renal or hepatic impairment N=54
1 10/20/97 11/25/97	543 1177-97-02.02	"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"	Open-label, Single-dose, Single-center	PK, Safety, Dialysis Clearance (No Imaging)	Adults with ESRD on Hemodia-lysis N=8
1+ 05/23/94 06/30/94	1177-01+ 1177-01+	"A Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers"	Double-blind, Placebo-controlled, Ascending dose (single)	PK, Safety, Tolerance (No Imaging)	Adults-Normal Volunteers N=16
1** Ongoing	[redacted]	[redacted]			

* Start = date the first patient was enrolled / initiation date (per Sponsor)
@ End = date the last patient was discharged from study / completion date (per Sponsor)
+ Study conducted in Japan; the Sponsor stated that the safety data from this trial could not be integrated with those of the US studies
**Study on-going; not part of this application/review.

OVERVIEW OF PHASE 2 STUDIES:

- The Sponsor conducted six Phase 2 studies in 355 patients at doses of 0.1, 0.2, 0.3, 0.4, or 0.5mmol/kg OptiMARK™ for several MRI indications. Each of these studies was similar in design, sharing double-blind, randomized, "pseudo cross-over" [p. 1.0367, Vol. 2.2] features. A total of 354 patients each received two injections of OptiMARK™ separated in time by 1 to 7days and are therefore reported twice in the safety summary data (i.e., 729 exposures to the drug).
  1. Study # 464 was for MRI of the brain
  2. Study # 465 was for MRI of the spine
  3. Study # 467 was for MRI of the liver
  4. Study # 466
  5. Study # 468
  6. Study # 469 was for MRI of the musculoskeletal system

- The Sponsor has chosen not to pursue at this time so only the safety data from these trials is included with the NDA.
- The table below projects an overview of the Phase 2 studies:

OVERVIEW: PHASE 2 STUDIES: OptiMARK™ : NDA # 20937

Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed
2 11/18/93 12/15/94	464 1101-02	"Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Brain"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between first and second dose)	Safety, Tolerance, Efficacy	Adults with known or suspected CNS pathology N=83
2 01/18/94 03/13/95	465 1101-03	"A Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Spine and/or Associated Tissue"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between, first and second dose)	Safety, Tolerance, Efficacy	Adults with known or suspected Spine pathology N=89
2^ 06/08/94 03/14/96	466^ 1101-04.02^	A Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Breast"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between first and second dose)	Safety, Tolerance, Efficacy	Adults with known or suspected Breast pathology N=36
2 05/01/94 11/03/94	467 1101-05.01	"A Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Liver"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between first and second dose)	Safety, Tolerance, Efficacy	Adults with known or suspected Liver pathology N=86

* Start = date the first patient was enrolled / initiation date (per Sponsor)
@ End = date the last patient was discharged from study / completion date (per Sponsor)
^ "Mallinckrodt Medical, Inc. has chosen not to pursue the indications at this time and has only reported safety data from these studies in the respective clinical study reports and Integrated Summary of Safety ..." [p. 1.0367, Vol. 2.2]

OVERVIEW OF PHASE 3 STUDIES

- The Sponsor carried out 8 Phase 3 studies in 1064 patients. The two identical open-label CNS studies (Study # 484 and 485) and the two identical open-label liver studies (Study # 486 and 487) were terminated by the Sponsor prior to completion.
- All four of the Pivotal Phase 3 studies (Studies # 488, 525, 490 and 526) were similar in design, analysis, and endpoints.
- The table below projects an overview of the Phase 3 studies:

OVERVIEW: PHASE 3 OPEN-LABEL STUDIES: OptiMARK™ : NDA # 20937

Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed
3% 9-29-1995 2-23-1996	484 & 485% 1177-95-02.01	"A Multicenter, Open-label Study to evaluate the Safety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) in MRI of the Central Nervous System"	Open-label, Single-dose, Multi-center,	Safety, Tolerance, Efficacy	>2 years with Known or suspected lesions of brain or spine N = 15 + 39
3% 04/16/95 05/02/96	486 & 487 % 1177-95-02.01 %	"A Multicenter, Open-Label Study to Evaluate the Safety, Tolerance, and Efficacy of OptiMARK™ (Gadoversetamide Injection) in MRI of the Liver"	Open-label, Single-dose, Multi-center,	Safety, Tolerance, Efficacy	>2 years with Known or suspected lesions of liver N = 98 + 122

* Start = date the first patient was enrolled / initiation date (per Sponsor)
@ End = date the last patient was discharged from study / completion date (per Sponsor)
%"Two open-label CNS studies (Study 484 and 485) and two open-label liver studies (Study 486 and 487) were terminated prior to completion of enrollment in order to incorporate the FDA-suggested study design modifications including a comparator group (i.e., Magnevist®) and overall analytical plan to demonstrate equivalence to the approved comparator"[p1.0378, Vol. 2.2]
** "These studies were similar in design with common clinical safety monitoring (vital signs, physical exams, ECG's, clinical laboratory parameters, injection tolerance and adverse events) and with generally similar inclusion and exclusion criteria." [p. 1.0379, Vol. 2.2]

APPEARS THIS WAY
ON ORIGINAL

OVERVIEW: PHASE 3 PIVOTAL STUDIES: OptiMARK™ : NDA # 20937					
Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed
3 Pivot-al ** 1-15-1996 5-31-1997	488 & 525 ** 1177-95-03.03 **	"A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) Compared to Magnevist® (Gadopentetate Dimeglumine Injection) in Patients with Central Nervous System Pathology"	Randomized Double-blind, Multi-center, Parallel-group, Single-dose, comparing OptiMARK™ and Magnevist®	Safety, Tolerance, Efficacy	Adults with known or suspected CNS pathology N = 201 + 194
3 Pivot-al ** 2-5-1996 4-29-1997 & 8-20-1996 6-3-1997	490 & 526 ** 1177-95-05.03 **	"A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) Compared to Magnevist® (Gadopentetate Dimeglumine Injection) in Patients with Liver Pathology"	Randomized Double-blind, Multi-center, Parallel-group, Single-dose, comparing OptiMARK™ and Magnevist®	Safety, Tolerance, Efficacy	Adults with known or suspected liver pathology N = 202 + 193

* Start = date the first patient was enrolled / initiation date (per Sponsor)
@ End = date the last patient was discharged from study / completion date (per Sponsor)
"Two open-label CNS studies (Study 484 and 485) and two open-label liver studies (Study 486 and 487) were terminated prior to completion of enrollment in order to incorporate the FDA-suggested study design modifications including a comparator group (i.e., Magnevist®) and overall analytical plan to demonstrate equivalence to the approved comparator"[p1.0378, Vol. 2.2]
** "These studies were similar in design with common clinical safety monitoring (vital signs, physical exams, ECG's, clinical laboratory parameters, injection tolerance and adverse events) and with generally similar inclusion and exclusion criteria." [p. 1.0379, Vol. 2.2]

- Clarification: It is appropriate to clarify the extent of exposure at this time for this program because the Sponsor states (on p. 1.0348, Vol. 2.2, and in other parts), "A total of 2038 subjects or patients were exposed to study drug or placebo ...".
  The actual breakdown is: 1309 OptiMARK™ (number of patients = 1309, number of exposures = 1663 because 354 patients received two doses) and these are the critical numbers: 329 Magnevist®, 46 placebo→ 1684 subjects participating in all the studies combined and 2038 is total number of exposures to all agents (including placebo and Magnevist®). In short, 2038 is not the number of subjects but the number of total exposures of OptiMARK™ (1663) + Magnevist® (329) + Placebo (46). Recommendation to incorporate this in the labeling is necessary.

MATERIAL REVIEWED

The material/s reviewed were:
NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with (Volumes # M7.1 - M7.3), (BM),

This reviewer has commented on the following:

1. CNS Efficacy and related material including the pivotal phase 3 CNS studies (488 and 525, non-pivotal phase 3 CNS studies (484 and 485-not submitted for review), phase 2 CNS studies (464 and 465)
2. Safety for the entire program (all 19 trials)

These are presented as follows:

1. Efficacy reports (CNS) consisting of an overview, summary and conclusion.
2. Safety report (for the entire clinical program) consisting of an overview, summary and conclusion.
3. Complete Phase 1 trial reports for 433, 538, 489, 543, 1177 (Japanese study) presented as a synopsis for each trial.
4. Complete Phase 2 trial reports for CNS studies 464 and 465 presented as a synopsis for each trial.
5. Complete Phase 3 open-label reports for CNS studies 484 and 485 presented as a combined synopsis (as presented by the Sponsor).
6. Complete Phase 3 pivotal reports for CNS studies 488 and 525 presented as a synopsis for each trial.

SOME GENERAL COMMENTS ON THE APPLICATION

1. This application was well organized as a package, and the presentation within each trial was uniformly systematic. Information could be retrieved with ease. Communication and correspondences were appropriate and timely. Responses to questions were appreciably timely.
2. Data and information from the preclinical and PK studies are adequate and informative clinically (see appropriate reviews)
3. Subject numbers and monitoring for purposes of safety were adequate, except for EKG parameter (see safety comments). But the bulk of the data was presented without baselines.
4. The extent of exposure was adequate.
5. Acceptable parameters for each safety monitoring were chosen (e.g. vital signs) except for EKG, although some of the parameters (e.g. adverse event categorization, clinical significance categorization, etc) were on a subjective scale. Minor deficiencies in lab parameters were noted (e.g. urinalysis, absence of glucose or bicarbonate). Selected EKG parameters and adequacy (on several issues) were the

major concerns (see safety report). Vital signs did not include temperature recordings on any patient in any trial.

6. Within the trials, similar parameters and definitions were implemented and were maintained through out the clinical trials (except the Japanese study), making the review process easier. However, at times these were used inter-changeably (e.g. serious and severe). More than adequate statistical data was incorporated but the bulk of it was not presented in a clinically relevant and interpretable manner (e.g., no baseline values, changes presented as a shift from a range, etc.). Additionally, the agency Statistician recognized that some of the methods chosen by the Sponsor were unique to this application and some methods were not proposed during planning, but were implemented in the analysis (for the efficacy data).
5. Difficulties were experienced and encountered in backtracking of an abnormal parameter from the summary safety volumes/shift tables/other integrated data to the individual patient/s or even to a study at times.
6. Significant (typographical and reporting) differences were observed in description of the serious adverse events (amongst others) between the respective clinical volume and the ISS volume for all of the 8 reported serious adverse events.
7. Specific comments have been made through out the review in the respective sections.

FINAL CONSIDERATIONS (OPTIONS)

CNS EFFICACY*

[*See Efficacy Report pages 152-162 for complete details]

1. Non Approval for CNS Efficacy or

2. Conditional Approval for CNS Efficacy (if the equivalence interval is acceptable and ignoring selection bias & non-representative patient population/patient enrichment), to incorporate the following (that is only scientifically fair and ethical):

a) OptiMARK™ is indicated in patients with known CNS pathology (particularly post treatment patients) and exclusion of 'highly suspected' or 'thought to have' from proposed indication and labeling; and or
b) Contrast MRI with another approved agent is required when OptiMARK™ is used.

SAFETY*

[*See Safety Report pages 163-218 for complete details]

1. Non Approval based on EKG safety concerns or

2. Conditional approval provided the Sponsor is able to demonstrate adequacy, completeness, and reader appropriateness using acceptable parameters for the existing records (retrospective). This would obviously overlook the concern of the lack of adequate frequency (timing). The outcome of these may call for additional recommendations.

3. Conditional approval (pending 2 above) with labeling (in addition to the proposed labeling) to indicate:

a) Caution in patients with known or pre-existing seizure disorder, renal disorder, liver disorder
b) caution to indicate possibility of bradycardia and potential EKG changes
c) caution to indicate possibility of increased risk of developing adverse event if one has history of an allergic reaction to iodine or other contrast agents
d) caution to indicate that greater frequency and severity of adverse events was noted with higher doses
e) caution to indicate that patients with renal disease may experience delayed cardiac arrhythmias
f) caution/warning to indicate possibility of transient lab errors- calcium, iron, ferritin
g) caution/warning to reflect that drug-drug interaction has not been studied
h) caution/warning on fertility, carcinogenicity, pregnancy, lactation/breast feeding
i) caution/warning that pediatric patients have not been studied
j) caution/warning that repeat dosing has not been tested
k) caution/warning to indicate that the incidence or severity of the adverse events could potentially be greater than what is projected (referring to the trials during which time a significant number of patients were on steroids and or antihistamines

RECOMMENDATION

1. Non Approval for CNS Efficacy:
   The Sponsor has not adequately demonstrated efficacy (for CNS indication) in terms of equivalence to Magnevist® in a scientific and unbiased manner largely due to a non-representative enriched patient population and
   The Sponsor has not adequately demonstrated efficacy (for CNS indication) in terms of equivalence to Magnevist® when an equivalence interval of +1.5 to –1.5 is not used.
2. Non Approval for Safety:
   The Sponsor has not demonstrated adequate safety monitoring, specifically, EKG.

/S/ MD

Ramesh Raman, M.D.
(Medical Officer)

/S/ 12/4/98

Eric A. Jones, M.D
(Medical Team Leader)

END OF REGULATORY OVERVIEW

NDA # 20 937
IND [redacted]

OptiMARK™

Report # 433/Phase 1
Protocol # 1101-01

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
- Primary Volumes for this study: 2.10 and 2.11

OVERVIEW: 433-PHASE 1 STUDY*: OptiMARK™ : NDA # 20937					
Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed (N= 16 + 4)
1 03/01/93 04/30/93	433 1101-01	"Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal, Healthy Male Volunteers"	Ascending dose PK study Placebo-controlled	Safety, Tolerance, First-in-human study	Normal Adult Volunteers

*This was the 'first-in-human' study for this drug involving 'only' male subjects.

The original protocol dated Jan 8, 1993 was amended twice. The first amendment included addition of 24-hr pre-injection and 7- day post-injection sperm count analysis. The second amendment refined these specifications further. The sperm count assessments are not mentioned in the study proposal and therefore, the reviewer has not commented on this in the study protocol review section.

The comments on the pharmacokinetics for this phase 1 PK study is brief (see comments by the pharmtox/biopharm reviewers). The comments on the safety section are abbreviated. Detailed comments have been made in the over-all safety review section.