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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Pharmacology Review(s)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160.

Reviewer: **David E. Bailey, Ph.D.**

Review: **#3**

NDA Number: **20-937**

Submission:

Designation	Letter Date	Stamp Date	Contents
SE8 003 PA	29-MAR-2002	01-APR-2002	PRIOR APPROVAL SUPPLEMENT Use of power injector

Information to Sponsor: Yes ( ) No (XX)

Draft Completion Date: November 29, 2002
Completion Date: December 13, 2002

Sponsor:
Mallinkrodt Inc.
P. O. Box 5840
675 McDonnell Blvd.
St. Louis, MO 63134
Telephone: 314-654-6061
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Sponsor Representative:
Edward R. Porter
Senior Regulatory Affairs Associate

Drug Name: OptiMARK®

INTRODUCTION

OptiMARK® (Gadoversetamide Injection) is a nonionic linear gadolinium chelate approved for use as an intravenous MRI contrast agent. It is a sterile, nonpyrogenic, 0.5 mmol/mL aqueous formulation. The approved dose is 0.1 mmol/kg to be administered at a rate of 2 mL/sec from a hand held syringe. The Sponsor is seeking approval for the use of a power injector for administration of the drug.

The Sponsor conducted a dog study to support the safety of using the power injector in clinical trials. This study was conducted prior to initiation of the clinical trials, and was submitted to IND 41,534 on January 17, 2001. The protocol for the clinical studies was submitted at the same time the report for the dog study was submitted. The dog study was reviewed by Toxicology reviewer, John Melograna, and concluded that it was reasonably safe to allow the clinical studies to proceed. This conclusion was supported by the Pharmacology/Toxicology team leader, Nakissa Sadrieh. However, a written review of the dog study was never completed.

The dog study is the subject of this review.

TOXICOLOGY STUDY

Study Title: The assessment of cardiovascular changes caused by injecting Optimark at elevated rates of administration in the anesthetized dog. (This study was conducted in 2 parts, Part 1 and Part 2.)

Laboratory: Mallinkrodt Inc., Biological Sciences Section, St. Louis, MO

Report Number: 1101/99/100-E

Report Date: April 28, 2000

In-Life Study Dates: Not indicated.

GLP Compliance: Not required.

Device: Optistar MR Injector System, approved December 6, 1999, 501(k) Approval Number K-984088.

PART 1

Design: This study was designed to evaluate the cardiovascular effects of using a power injector to administer OptiMARK at dosages of 0.3 mmol/kg and 0.6 mmol/kg and at rates of administration of 1.0, 3.0 and 10.0 mL/sec. The approved dosage is 0.1 mmol/kg and approved rate of injection with a hand held syringe is 2.0 mL/sec. In this study, 8 anesthetized male Beagle dogs were administered each of the following treatments in a randomized cross over design with at least 45 minutes between treatments.

Designation	Treatment
A	OptiMARK at 3 mL/sec with hand held syringe
B	Saline at 10 mL/sec with Power Injector
C	OptiMARK at 1 mL/sec with Power Injector
D	OptiMARK at 10 mL/sec with Power Injector

Parameters recorded included: ECG (PR and QT intervals), heart rate, and blood pressure which were recorded prior to injection, at the completion of injection, and at 0.25, 0.50, 1, 3, 5, 10, 15, and 30 minutes after injection.

RESULTS:

Blood Pressure: With all treatments that received OptiMARK, blood pressure started falling even during injection, and a statistically significant decrease (19-28%) was observed when compared to saline controls. However, all values returned to baseline within 1-5 minutes of completion of injection. None of the animals or treatments elicited blood pressure changes that lasted longer than 5 minutes. Saline injections had essentially no effect on blood pressure. The magnitude of blood pressure change was independent of rate of injection. The table below shows summary values for blood pressure.

Blood Pressure (Systolic/Diastolic in mmHg)

OptiMARK Treatment	Baseline	Peak Value	Change from Baseline Value
	1.0 mL/sec		
Saline (1.2 mL/kg)	126/78	116/73	-10/-5
0.3 mmol/kg	122/75	88/55	-34/-20*
0.6 mmol/kg	134/89	109/71	-25/-18*
	3.0 mL/sec		
Saline (1.2 mL/kg)	126/78	116/73	-10/-5
0.3 mmol/kg	125/76	100/58	-25/-18*
0.6 mmol/kg	124/82	100/62	-24/-20*
	10.0 mL/sec		
Saline (1.2 mL/kg)	126/78	116/73	-10/-5
0.3 mmol/kg	124/74	96/56	-28/-18*
0.6 mmol/kg	129/80	104/61	-25/-19*

Heart Rate: With all treatments that received OptiMARK, heart rate started falling even during injection, and a statistically significant decrease (9-13%) was observed when compared to saline controls. The maximum reduction in heart rate was seen at 15-30 seconds after completion of injection and values had returned to baseline values by 1 minute. Saline injections had essentially no effect on heart rate. The magnitude of heart rate change was independent of rate of injection. The table below shows summary values for heart rate.

Heart Rate (Beats/min)

OptiMARK Treatment	Baseline	Peak Value	Change from BaselineValue
	1.0 mL/sec		
Saline (1.2 mL/kg)	146±14	142±9	-4±0
0.3 mmol/kg	150±14	131±11	-19±4*
0.6 mmol/kg	148±10	132±13	-16±3*
	3.0 mL/sec		
Saline (1.2 mL/kg)	146±14	142±9	-4±1
0.3 mmol/kg	139±15	127±11	-12±4
0.6 mmol/kg	142±7	129±12	-13±2*
	10.0 mL/sec		
Saline (1.2 mL/kg)	146±14	142±9	-4±0
0.3 mmol/kg	145±7	129±5	-16±3*
0.6 mmol/kg	141±10	128±9	-13±4*

ECG (PR Interval): For all treatments the PR interval increased 4-8 msec (5-9%) over baseline values, but none of the increases were statistically significant when compared to individual baseline values or to saline control values. None of the treatments of 0.3 or 0.6 mmol/kg at 1, 3 or 10 mL/sec injection rate had any effect on the length of PR interval. The table below shows summary values for PR interval.

PR Interval (msec)

OptiMARK Treatment	Baseline	Peak Value	Change from Baseline Value
	1.0 mL/sec		
Saline (1.2 mL/kg)	91±6	99±7	8±2
0.3 mmol/kg	91±6	97±5	6±1
0.6 mmol/kg	90±3	98±5	8±1
	3.0 mL/sec		
Saline (1.2 mL/kg)	91±6	99±7	8±2
0.3 mmol/kg	92±8	100±12	8±2
0.6 mmol/kg	91±5	95±10	4±5
	10.0 mL/sec		
Saline (1.2 mL/kg)	91±6	99±7	8±2
0.3 mmol/kg	94±7	98±8	4±2
0.6 mmol/kg	88±6	95±8	7±4

ECG (Corrected QT Interval): For all treatments the Corrected QT interval increased 4-13 msec (1-4%) over baseline values, but none of the increases were statistically significant when compared to individual baseline values or to saline control values. None of the treatments of 0.3 or 0.6 mmol/kg or 1, 3 at 10 mL/sec injection rate had any effect on the length of QT interval. The table below shows summary values for Corrected QT interval.

Corrected QT Interval (msec)

OptiMARK Treatment	Baseline	Peak Value	Change from Baseline Value
	1.0 mL/sec		
Saline (1.2 mL/kg)	362±10	378±11	16±3
0.3 mmol/kg	309±21	313±20	4±2
0.6 mmol/kg	357±19	361±17	4±2
	3.0 mL/sec		
Saline (1.2 mL/kg)	362±10	378±11	16±3
0.3 mmol/kg	329±20	329±15	0±4
0.6 mmol/kg	383±6	387±7	4±2
	10.0 mL/sec		
Saline (1.2 mL/kg)	362±10	378±11	16±3
0.3 mmol/kg	311±19	315±17	4±2
0.6 mmol/kg	354±18	367±14	13±4

PART 2

Design: This study was designed to compare the cardiovascular effects of 4 approved gadolinium contrast agents at increased dose and rate of injection. OptiMARK, Magnevist, ProHance, Omniscan and Saline were all administered to each of 5 dogs in a randomized Latin Square design with at least 45 minutes between doses. The agents were all administered at a dose of 0.6 mmol/kg and at a rate of 3 mL/sec. Saline dose was 1.2 mL/kg and rate was also 3 mL/sec.

Parameters recorded included: ECG (PR and QT intervals), heart rate and blood pressure, and were recorded prior to injection, at the completion of injection, and at 0.25, 0.50, 1, 3, 5, 10, 15, and 30 minutes after injection.

Results: Individual data are not presented for this comparative study. This part of the study has no relationship to the rest of the study and really is not pertinent to the evaluation of the effects of using the power injector for higher rates of administration of OptiMARK up to 10 mL/sec. For the drugs administered, the values for heart rate and blood pressure returned to baseline within 1-5 minutes for OptiMARK, Magnevist, and Omniscan. However, for Prohance, heart rate and blood pressure values did not return to baseline values even after 30 minutes of monitoring. Values were not recorded beyond 30 minutes. From ECG tracings, none of the four agents had any effect on PR or QT intervals.

OVERALL SUMMARY:

OptiMARK® (Gadoversetamide Injection) is a nonionic linear gadolinium chelate approved for use as an intravenous MRI contrast agent. It is a sterile, nonpyrogenic, 0.5 mmol/mL aqueous formulation. The approved dose is 0.1 mmol/kg to be administered at a rate of 2 mL/sec from a hand held syringe. The Sponsor conducted a dog study designed to evaluate the cardiovascular effects of using a power injector to administer OptiMARK® at dosages of 0.3 mmol/kg and 0.6 mmol/kg and at rates of administration of 1.0, 3.0 and 10.0 mL/sec. Effects were compared to saline controls administered at the same rate of injection. Anesthetized male Beagle dogs were administered each of the treatments in a randomized cross over design with at least 45 minutes between treatments. Heart rate and blood pressure decreased in all groups receiving OptiMARK® at all dosages and rates of administration. These effects were not dependent on rate of injection. ECG intervals (PR and Corrected QT) were not altered by any of the treatments.

Based on the results of this study, cardiovascular effects were not different for animals receiving OptiMARK® at increased rates of administration up to 10 mL/sec by power injector, than were seen at the approved administration rate of 2 mL/sec from hand held syringe.

Not Studied

CONCLUSION:

Based on the nonclinical pharmacology and toxicology study reviewed above, administration of OptiMARK® at the rate of up to 10 mL/sec by use of a power injector, had no effect on ECG tracings (PR and QT intervals) in anesthetized dogs. Heart rate and blood pressure were reduced at all concentrations of OptiMARK® (0.3 and 0.6 mmol/kg, 3 and 6X the approved concentration) and at all rates of injection. These decreases in heart rate and blood pressure were independent of rate of injection from ½X (1.0 mL/sec) to 5X (10 mL/sec) the approved rate of injection of 2 mL/sec.

Therefore, from the perspective of nonclinical pharmacology and toxicology, use of the power injector is approved for use in the administration of OptiMARK® (Gadoversetamide Injection).

REVIEWER: /S/

David E. Bailey, Ph.D.

Date

TEAM LEADER CONCURRENCE: /S/

Adebayo A. Laniyonu, Ph.D.

Date

DRAFT COMPLETION DATE: November 29, 2002

COMPLETION DATE: December 13, 2002

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/s/

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