CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Administrative Documents

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2003

To: Edward Porter	**From:** James Moore
Company: Mallinckrodt, Inc.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (314) 654-3344	**Fax number:** (301) 480-6036
Phone number: (314) 654-6061	**Phone number:** (301) 827-7510

Subject: Approval Letter and Draft Labeling

Total no. of pages including cover: 18

Comments: Attached is the approval letter and draft labeling for

NDAs 20-937/20-975/20-976/S003.

Document to be mailed: ☑ YES ☐ NO

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-937/ 20-975	Efficacy Supplement Type SE-8	Supplement Number 003
Drug: OptiMARK®	Applicant: Tyco/Mallinckrodt Health Care	
RPM: James Moore	HFD-160	Phone # 827-7510
Application Type: (x) 505(b)(1) ( ) 505(b)(2)	20-937/ OptiMARK® Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	February 1, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review N/A
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified N/A
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified by reference
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(I)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1)

	( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A
❖ Exclusivity Summary (approvals only)	N/A
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X December 31, 2002
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE ( )
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	x-See medical review
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	

• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	x-November 29, 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Not yet Done
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
Biopharmaceutical review(s) *(indicate date for each review)*	N/A
Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable N/A ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested N/A ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X December 13, 2002

Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

APPEARS THIS WAY
ON ORIGINAL

DIVISION MEMO TO THE FILE

NDA:	20-937 (Parent NDA in Glass Vials)
	20-975 (Pharmacy Bulk Pack)
	20-976 (Plastic Syringes)
DRUG:	OptiMARK Injection
CLASS:	Gadolinium Contrast Agent
ROUTE:	Intravenous
INDICATION:	Contrast Enhancement of the CNS and Liver
MODALITY:	Magnetic Resonance Imaging (MRI)
CATEGORY:	Efficacy Supplement
SPONSOR:	Tyco Healthcare
SUBMITTED:	March 29, 2002
PDUFA:	February 1, 2003

RELATED REVIEWS:

Clinical:	Dr. Zolman
Pharm/Tox:	Dr. Bailey
Statisitical:	Dr. Sobhan

RELATED DRUGS: Magnevist, Omniscan and Prohance

Background:

OptiMARK is a gadolinium based contrast agent for Magnetic Resonance Imaging (MRI) which was approved in 1999. It is one of four gadolinium contrast agents marketed in the United States. OptiMARK is approved for use with MRI for imaging the CNS and liver to facilitate visualization of lesions with abnormal vascularity or abnormal blood brain barrier. At the time the NDA was approved, there was a Phase 4 commitment to complete additional studies (pre-clinical and clinical) to evaluate the relationship of OptiMARK to QT/QTc abnormalities that were observed in adults[1]. To date, the clinical trial has been completed, however, the results have not been submitted. The pre-clinical study is still ongoing. Currently under the "Precautions" section of the label the following exists:

"Electrocardiographic changes

ECG parameters for the 0.1mmol/kg dose were monitored in 93 subjects (6 volunteers and 87 patients) at multiple time points within the first day (immediate, 15, 30, 60 and 120 minutes and at 24 hours) of OptiMARK Injection. Continuous ECG monitoring was not obtained. In these subjects, QT/QTc prolongations of ≥ 30 ≤ 60 msec and prolongations of ≥61 msec were reported in 15 and 3 subjects respectively. None of the prolongations were found to be associated with malignant arrhythmias.

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[1] Phase 4 commitments as reported in the Action letter dated December 8, 1999:
a)"Pre-clinical cardiac electrophysiologic studies: These studies will evaluate action potential and electrophysiologic channel blocking in appropriate animal models. A wide range of doses will be studied to provide an adequate margin of safety based on body surface area conversion" and,
b)"Expanded clinical electrocardiographic monitoring: These studies will be conducted over a wide range of gadoversetamide doses. All patients will have continuous, comprehensive electrocardiographic monitoring"

Similar QTc prolongations were noted in patients who received placebo and other doses of OptiMARK Injection, however; the studies were not designed to establish causal relationships. The effect of dose, other drugs and other medical conditions were not studied. Caution should be exercised in patient who may be using medication or who may have underlying metabolic, cardiac, or other abnormalities that may predispose to cardiac arrhythmias."

Introduction:

The Sponsor has submitted a pre-clinical cardiovascular safety study and a single clinical trial. The intent of the submission is to provide safety data to support the administration of OptiMARK via a power injector. The current approved dose of OptiMARK is 0.2mL/kg (0.1mmol/kg) administer intravenously (manually) at a rate of 1-2mL/sec (maximum labeled dose is 30mL). Under the "Dosage and Administration" section, the label explicitly states that "This product has not been evaluated for use in magnetic resonance angiography or for drug delivery by power injection." Typically angiographic imaging requires fast injection rates for a tight bolus delivery. Angiography may also require larger volumes (depending upon the body system under investigation) than what are currently approved. Thus the above statement was made in the label at the time of drug approval. Original drug approval for both CNS and liver did not require such fast or tight bolus drug delivery as evidenced by the labeled rate of 2mL/sec. The Sponsor has not provided the rationale for the study of power injector use for the current approved indications. Intuitively, however, convenience of administration and uniformity of administration may be practical reasons for such study. More importantly, the Sponsor has not provided the rationale for using higher rates of injection than are currently approved (See Table 1 for a list of study groups). The impact of higher rates of injection on efficacy and image methodology (timing) was not the subject of study in this clinical trial. It is anticipated that there are literature data on the general benefits but these were not submitted. Thus the data submitted at these higher rates do not support labeling changes with respect to the rate of injection.

TABLE 1: Dose Administration under Review in this Submission

Treatment Group*	Study Agent	Injection Rate	Injection Method
1	OptiMARK[1]	2mL/sec	Power
2	OptiMARK[1]	4mL/sec	Power
3	OptiMARK[1]	6mL/sec	Power
4	Saline[2]	2mL/sec	Power
5	Saline[2]	4mL/sec	Power
6	Saline[2]	6mL/sec	Power
7	OptiMARK[1]	2mL/sec	Hand

* 20 subjects per treatment group, 1= 0.1mmol/kg OptiMARK (0.2mL/kg), 2= 0.2mL/kg of Saline
Shading denotes approved dose, Table source: Dr. Zolman's review page 14.

This review will highlight the findings of the preclinical trial and then focus on the comparison of the 2mL/sec dose cohorts (Saline and OptiMARK) within the clinical trial. The burden of providing data to support the safety of this dose has already been met, by the original NDA. The introduction of the power injector (at same dose and rate) would appear to have minimal clinical consequences. Thus, the evidence that is required to support this claim is considered minimal. Therefore, assessment will be limited to the identification of trends with particular focus on the occurrence of adverse events.

Preclinical:
The pre-clinical study in dogs assessed the cardiovascular safety of the administration of 3 and 6 times (0.3mmol/kg and 0.6mmol/kg respectively) the current approved dose at half, 1.5 and 10 times (1 mL/sec, 3mL/sec and 10mL/sec respectively) the approved rate. The 1.5mL/sec was delivered by hand, all other rates were delivered by power injector. As reported by Dr. Bailey there were no adverse effects on ECG tracings with OptiMARK administration up to a rate of 10mL/sec given by power injector. Although heart rate and blood pressure changes were observed to decrease following all OptiMARK injections at the studied concentration, the effects were noted to be independent of the rate of injection. As per Dr. Bailey's review, the findings for OptiMARK injection at higher rates were no different from those seen at the approved rate of 2mL/sec. Dr. Bailey has recommended approval for the OptiMARK with a power injector.

Clinical:
The value of the safety data base is limited by the sample size. The calculation of sample size was based upon the probability of a rare cardiac event [2] occurring. On page 1.159 of the submission, the Sponsor states that in previous dosing experience, 20 cardiac adverse events (not necessarily rare) were reported in 2000 administrations, thus implying an event rate for **any** cardiac event to be 1%. The Sponsor, however, used a 10% event rate to power this study based on the occurrence of a **rare** cardiac event. If a 1% event rate is used, a cohort sample size of 20 would provide for an 18% chance of seeing at least one rare cardiac event. If one were to further pool all of the OptiMARK cohorts (sample size of 80), the probability of seeing a rare cardiac event is still only 55%. In addition, since only **healthy** subjects were studied, the probability of a rare cardiac event may even be lower than 1% in this population. Overall the study was not adequately powered to show a difference in safety between cohorts (different rates of injection) even if a difference truly existed. In addition, the safety of the higher rates of injection would require study in a **patient** population.

[2] Rare cardiac event is identified as any one of the following: Heart Rate > 100bpm, PR Interval >200msec, QTc change from baseline > 60mesec, QTc value > 45msec, QRS > 100msec, Change in T wave morphology or U wave presence

The FDA is in the process of drafting guidelines for assessing QT interval prolongations. It is clear that the scientific approach to this issue is evolving and thus recommendations for trial design are changing. At a recent meeting[3] where the draft consensus ICH guideline was discussed, it was clear that the scientific community is concerned about the potential clinical consequences of drug-induced prolongations of less than 60 msec.

1. **Adverse Events (AE):**

Of the 140 subjects receiving drug or placebo, 43 subjects reported 64 adverse events. Of the 80 subjects receiving OptiMARK, 26 subjects experienced 39 adverse events. The most common adverse events reported for the OptiMARK group were taste perversion 9/80 (11.3%), warm sensation 6/80 (7.5%), dizziness 4/80 (5%) and headache 3/80 (3.8%). No adverse events were considered serious. As the rate of injection increased, the number of subjects experiencing an AE and the number of AEs increased. Both the digestive and skin/appendage body systems had AEs reported in the 4mL/sec group or higher. AEs related to the digestive system were only seen in the two high rate Saline groups (Please see Dr. Zolman's Tables 2 and 3). To look at potential relationship of rate injection to the occurrence of an adverse event, the Sponsor looked at AEs occurring within 15 minutes of dosing. A total of 35 AEs were reported within the first 15 minutes post-dosing across all treatment groups. Please see Table 2 for the breakdown by treatment group. Of the 35 AEs identified, 7 were injection site pain or reaction. Two of the 7 injection site reactions occurred in the OptiMARK 6mL/sec group and the remainder occurred across the three placebo groups. None of the injection site AEs required treatment.

TABLE 2. Number of Subjects with an AE Reported Within the First 15 Minutes of Dose.

Injection rate	OptiMARK		Saline
	Hand	Power	Power
2mL/sec	3/35	3/35	3/35
4mL/sec	N/A	6/35	3/35
6mL/sec	N/A	10/35	7/35

Data Source: Submission Dated 3/29/02, Vol. 6, pages 6.185-6.187.

Compared to the OptiMARK NDA database, there were no new types of adverse events reported as a result of this study. Overall the AE profile is similar to that of the NDA database. No significant difference is seen between the saline and OptiMARK groups. The adverse event rates across the 2mL/sec cohorts were comparable. No trends can be identified other than the fact that as rate increased, the number of adverse events increased.

[3] Drug Information Association meeting: The Clinical Evaluation of QT Interval Prolongation and Proarrhythmic Potential for Non-Antiarrythmic Drugs, held January 13-14, 2003 in Rockville, MD.

The Office of Drug Safety was consulted to perform a review due to concerns about this class of drugs from the local injection site safety perspective. Proprietary data has shown at large volumes and fast rates, extrasvasation of the dose may pose a significant safety threat. The consult requested a review that focused on reported cases of phlebitis, thrombophlebitis, thrombosis and injection site reactions. Results of this review identified 2 cases of seizure, which is not a labeled event and one case of an injection site reaction. There was no reported morbidity related to the injection site reaction. Other event reports were present in the database, however, Dr. Bacsanyi confirms that these events are consistent with the labeled events.

2. Electrocardiograms:

Since cardiac safety (QTc) is an ongoing issue, I will briefly summarize the findings related to reports of arrhythmia. Cases of sinus bradycardia and sinus arrhythmia were reported. A total of 14 subjects were reported as having bradycardia (6 OptiMARK and 8 Saline). Most (6/7) of the OptiMARK cases had bradycardia present at the time of pre-dosing (minutes prior to contrast administration). Thus, the attribution to treatment group cannot be made. A total of 13 subjects (6 OptiMARK[4] and 7 Saline) experienced sinus arrhythmias. Of the 6 OptiMARK cases (Table 3), 5 occurred within the first 10 minutes of administration. For the saline group 4 out of the 7 occurred within the first 10 minutes of administration. Four out of the 6 cases reported after OptiMARK administration had sinus arrhythmia reported at one isolated timepoint. Of the two subjects experiencing sinus arrhythmia at multiple timepoints, subject (48120) received 2mL/sec by power injector and experienced sinus arrhythmia at 5, 20, and 25 minutes after OptiMARK administration. This subject had sinus bradycardia identified pre-dose and had stable QTc values (decreases of 10 msec or less as compared to pre-dose 2 read) at the time the sinus arrhythmia was reported. The second subject (48049) received 4mL/sec by power injector and experienced sinus arrhythmia at 1 minute, 1 and 4 hours after OptiMARK administration. Compared to the re-dose 2 QTc read, the subjects QTc values decreased by 13 msec for the 1 minute and 1 hour timepoint and increased by 13 msec (as compared to pre-dose) at the 4 hour timepoint.

TABLE 3: Subjects experiencing Sinus Arrhythmia

Injection rate	OptiMARK		Saline
	Hand	Power	Power
2mL/sec	2	1	4
4mL/sec	N/A	3	2
6mL/sec	N/A	0	1

Data Source: Sponsor Table 12.2.3-4 page 1.190.

Six subjects were reported as having T wave changes post treatment. Four occurred in the OptiMARK cohorts (2mL/sec and 4mL/sec power injector cohorts) and 2 occurred with saline (2mL/sec and 4 mL/sec cohorts).

[4] Sponsor reports 7 cases in Table 12.5.3-4 however in volume 8 page 8.101 Table 16.2.11-4, line listing reports "sinus rhythm".

All incidents for the OptiMARK cohorts were reported as isolated events occurring as early as 1 minute post dose and as late as 24 hours. Both Saline cases occurred at the 24 hour timepoint. None of the subjects with T wave changes had either sinus arrhythmia or sinus bradycardia reported. Overall, no definitive trends were identified.

Safety Update:
The Sponsor has submitted both adverse events from a clinical trial as well as post-market surveillance reports. The post-market surveillance reports identify an additional case of seizure that was not identified in Dr. Bacsanyi's review. The remainder of the adverse events reflect what has been previously reported in the label.

Conclusions:
This trial was not designed to support a label change for a higher rate of injection. The trial was not performed in a patient population requiring a higher rate, it was not adequately powered and the application did not provide either justification for use of a higher dose for the given indication or new efficacy data to support the higher rates. The trial does, however, support the use of a power injector at the current approved dose and rate.
The relationship of OptiMARK administration to QTc prolongation has yet to be determined. The Sponsor has completed their Phase 4 clinical trial, however, the results have not been submitted. Since this trial was designed prior to the draft ICH consensus guidelines on assessing QT interval prolongation, there is concern that the trial design may not be adequate to meet current guidelines. The Sponsor should submit the study results for review. Depending on the findings, additional studies may be needed.

Recommendation: Approval for use of power injector at the current dose and rate of injection.

Label:
Suggested changes include

- Remove the word "manually" from the dose and administration section.
- Delete the underlined portion of the following statement: "The product has not been evaluated for use in magnetic resonance angiography <u>or for drug delivery by power injector."</u>
- Add a statement to adverse event section about post-market surveillance reports of seizure.
- Add a paragraph in the clinical trial section describing the trial and findings including a statement that the safety and efficacy with the use of power injector at rates higher than 2mL/sec have not been established.

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

/s/

Sally Loewke
1/31/03 04:34:16 PM
MEDICAL OFFICER

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
On September 12, 2002, I called Edward Porter and requested volume 1.1 of NDA 20937 for supplement 003 a pending efficacy supplement.	NDA 20-937/20-975 S003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; **x FDA** — MADE: **X BY TELEPHONE**
	PRODUCT NAME Opptimark
	FIRM NAME Tyco/Mallinckrodt
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Edward Porter (314) 654-6061
SIGNATURE James Moore	DIVISION HFD-160

APPEARS THIS WAY ON ORIGINAL

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RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
On September 20, 2002, I called Mr. Edward Porter and requested a copy of the Safety Update. In a return voice mail message Mr. Porter said the Safety information would be sent.	NDA 20-937/20-975/SE8003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; **x FDA** — MADE: **X BY TELEPHONE**
	PRODUCT NAME: Optimark
	FIRM NAME: Tyco/Mallinckrodt Health Care
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Edward Porter (314) 654-6061
SIGNATURE James Moore	DIVISION HFD-160

APPEARS THIS WAY ON ORIGINAL

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RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
On September 19, 2002, I called Mr.Edward Porter of Tyco/Mallinckrodt and asked (1) if the device used in the trial for S003, N20-937 was an approved Device, (2) [redacted], (3) the location in the NDA of information on the Device used in the trial for the supplement under review. In a return call Mr. Porter said that the Device (Optistar) was approved [redacted] Mr. Porter also noted that information regarding the Device would be sent to the Division.	NDA 20-937/20-975/SE8-003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; **x FDA** — MADE: **X BY TELEPHONE**
	PRODUCT NAME: Optimark
	FIRM NAME: Tyco/Mallinckrodt Health Care

APPEARS THIS WAY
ON ORIGINAL

	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Edward Porter (314) 654-6061
SIGNATURE James Moore	DIVISION HFD-160

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RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
In response to Mr. Porter's question regarding the calculated review time for this supplement SE8003, NDA 20-937, I telephoned Mr. Porter on October 18, 2002, and left a voice mail message. In that message, I explained that the review time for the supplement would be 10 months because it was considered an efficacy supplement. Mr. Porter had expressed his opinion that the time should be less than 10 months because the supplement was only being reviewed for safety. I explained to Mr. Porter that the Agency doesn't distinguish between a review for Safety and Efficacy and a review for Safety with regard to review time. I reiterated that the review time for this supplement would be 10 months.	NDA 20-937/20-975/SE8 003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; x FDA — MADE: X BY TELEPHONE
	PRODUCT NAME: Optimark
	FIRM NAME: Tyco/Mallinckrodt Health Care

APPEARS THIS WAY
ON ORIGINAL

	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Edward Porter (314)654-6061
SIGNATURE James Moore	DIVISION HFD-160

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RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
On November 14, 2002, I called Mr. Edward Porter and clarified what was needed with regard to the Safety information and its format. In a voice mail message I stated that the information should be presented in the format it was submitted in the original NDA.	NDA 20-937/20975 SE8-003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; **x FDA** — MADE: **X BY TELEPHONE**
APPEARS THIS WAY ON ORIGINAL	PRODUCT NAME Optimark
	FIRM NAME Tyco/Mallinckrodt Health Care
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Edward Porter (314) 654-6061
SIGNATURE James Moore	DIVISION HFD-160

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RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 01/03/03
On December 23, 2002, I telephoned Mr. Edward Porter in response to a voice mail message he had left for me. Mr. Porter was not in when I placed the return call so I left a voice mail message for him. In that voice mail message, I restated that the Safety Update must be a separate and distinct submission and cannot be submitted as part of a periodic report. Later Mr. Porter called and stated that the Safety Update would be submitted during the first week of January, 2003. I also requested an electronic copy of the labeling for the product.	NDA 20-937/20-975/SE8-003
	IND NUMBER
	Telephone call
	INITIATED BY: APPLICANT/ SPONSOR; **x FDA** — MADE: **X BY TELEPHONE**
	PRODUCT NAME: Optimark
	FIRM NAME: Tyco/Mallinckrodt Health Care
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Edward Porter (314) 654-6061

APPEARS THIS WAY ON ORIGINAL

SIGNATURE James Moore	DIVISION HFD-160

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Internal Meeting to Discuss Progress and Timeline for Efficacy Supplement (SE8-003)
NDA 20-937/20-975, September 13, 2002, Conference Room 18B45, 1pm

Division Attendees:

Joseph Zolman, M.D., Ph.D., Clinical Reviewer, HFD-160
David Bailey, Ph.D., Pharmacology/Toxicology Reviewer, HFD-160
James Moore, R.Ph.,M.A., Project Manager, HFD-160

Background:

This meeting was scheduled to discuss the progress of the two disciplines on the review of this supplement, review times, and the development of a timeline for this supplement.

Discussion:

Pharmacology

The following questions were posed by the pharmacology reviewer:
(1) What is the supporting IND # for this application?
(2) Is the device being used in the trial approved?
(3) Where can information regarding the device be found in the NDA?
(4) Is there a description of the Device in the NDA?

Clinical

There are concerns about the following in this trial: (1) trial design (2) assessment of cardiac safety-QTc prolongation (3) small numbers of subjects included in the trial (4) conduct of trial (5) exclusion criteria (6) inclusion of only normal subjects in the trial. During the trial there was an increase in serum levels of several metals, but gadolinium was not measured.

The due date for the completion of the primary reviews was discussed. Both the clinical and the pharmacology reviewer stated that their reviews should be completed on or about the first week of December.

Action Items

(1) Verify IND # that supports this efficacy supplement.
(2) Contact company and inquire if the device used in the trial is an approved one, and where the information regarding the device may be found in the submission.
(3) Prepare and distribute timeline for the efficacy supplement.

The minutes were prepared by CAPT James Moore, Project Manager.

_____

James Moore,R.Ph., M.A.
Project Manager, HFD-160

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

/s/

James Moore
12/24/02 10:26:34 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Mallinckrodt Inc.
P. O. Box 5840
St. Louis, MO 63134

Attention: E. R. Porter

2. TELEPHONE NUMBER *(Include Area Code)*

(314) 654-6061

3. PRODUCT NAME

OptiMARK, Gadoversetamide Injection
NDA 20-976

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4250

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Edward R. Porter *Edward R Porter*	Manager, Regulatory Affairs	12/17/01

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

SECTION 2. LABELING

Mallinckrodt proposes that the data provided in this supplement supports revisions to the product labeling, specifically removal of the statement, "Has not been evaluated for drug delivery by a power injector."

Provided below are the proposed labeling revisions to the Package Insert.

OPTIMARK PI – MKG1177B99 REVISED 12/99

1 pages redacted from this section of the approval package consisted of draft labeling

Revise the text:

Mallinckrodt does not propose any changes to the OptiMARK container labels.

APPEARS THIS WAY
ON ORIGINAL

16 pages redacted from this section of the approval package consisted of draft labeling

See Medical Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Drug Safety

FROM: HFD-160 (Division of Medical Imaging and Radiopharmaceutical Drug Products) , James Moore, Project Manager

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT :	DATE OF DOCUMENT:
November 14, 2002		20-937, 20-975, 20-976	NDA Efficacy Supplement SE8-003	April 1, 2002

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
OptiMARK®	High	1C	January 14, 2003

NAME OF FIRM: Tyco/Mallinckrodt Health Care

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
E A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- xx SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: In reference to this NDA supplement to increase the rate of injection using an intravenous power injector, please provide a summary of adverse experience with OptiMARK®. In particular, we are looking for the following types of events: (1) phlebitis (2) thrombophlebitis (3) thrombosis (4) injection site reaction (5) pain at injection site and their relationship to the rate of injection, volume of injection or to the use of a power injector. Please provide hard-copies of the ts generated from this search.

cc: Original/ DFS/moore/kang/love/loewke/zolman/raman

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one):
James Moore	√ E-MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE *FOOD AND DRUG ADMINSTRATION*	**OPDRA POSTMARKETING SAFETY REVIEW**	
TO:	**FROM: Janos Bacsanyi, M.D.** **Division of Drug Risk Evaluation II(DDRE II) HFD- 440**	**OPDRA PID # D020502**
DATE REQUESTED: 11/14/02	**REQUESTOR/Phone #: James Moore**	
DATE RECEIVED: 11/14/02		
DRUG (Est): gadoversetamide	**NDA/IND # 20-976**	**SPONSOR** :Mallinckrodt
DRUG NAME (Trade): Optimark	**THERAPEUTIC CLASSIFICATION: NMR contrast agent**	

EVENT: phlebitis, thrombophlebitis, thrombosis, injection site reactions

Executive Summary: Inadvertent extravasation of magnetic resonance contrast media during intravenous injection can cause clinically significant damage. Catastrophic damage was experienced resulting in two amputations with the product Magnevist, these cases were likely initiated with some extravasation of contrast agent into the tissues. This issue has become more important in recent years, with the introduction of advanced imaging techniques. With the advent of contrast enhanced magnetic resonance angiography (CE-MRA), higher contrast doses, with injected volumes up to 60 mL, have been used more commonly.(1) The use of automated , power injector is also recommended in CE-MRA, increasing the chance for inadvertent extravasation of a large volume of contrast. The rate of injection may also be substantially higher than that commonly used in the past.

Reason for Request/Review: the sponsor submitted a supplement to increase the rate of injection by the use of an intravenous power injector.

Relevant Product Labeling:
In the Dosage and Administration section of the package insert it is stated that Optimark should be administered manually as a b eripheral intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg and a rate of 1-2 Ml/sec.
I ɔ stated that this product has not been evaluated for use in magnetic resonance angiography or for drug delivery by power injector.

Usage Information:

Search Date:	**Search Type(s):** **AERS** **Literature** Other

Search Criteria: Drug Names :Optimark (gadoversetamide)

MEDDRA Terms: All terms

Search Results: 6 cases were found: 2 reports concerned seizures. In one of them , a 38 year old female with M.S., suffered a cardiac arrest after extravasation of 4 mL contrast agent, CPR was done with success. The other seizure patient, a 52 year old male was intubated and admitted to ICU, where he made a complete recovery. Seizure is not a labelled event.
Injection site reaction ocurred in a 40 year old female, this was characterized as a large hot spot at the injection site, showing up 2 hours after the injection. This was accompanied by hives on her arm, spreading to the neck , chest and buttocks.There was inprovement on Benadryl therapy. Injection site reactions and urticaria are both labelled reactions.
The remainder of the reports consists of an allergic reaction with urticaria and periorbital edema, another patient with an anxiety reaction and one patient with nausea and vomiting.
All these patients received the recommended dose of the contrast agent and there was no indication that power injector was used.

Discussion / Conclusions:

A blinded animal study was reported in the literature where the relative toxicities of gadolinium products currently available in the United States were compared when extravasated in soft tissue. Of the four MR contrast agents, gadopentetate dimeglumine (Magnevist) caused the greatest tissue damage ,and gadoteridol and gadodiamide-the two lowest osmolar agents- the least. Gadoversetamide (Optimark) , which has an osmolality between Magnavist and the two other agents, caused a reaction that ıot be differentiated from that seen with gadopentate dimeglumine for both necrosis and edema.

. sk of tissue damage due to extravasation is not widely appreciated for the gadolinium products. Care should be exercised during contrast injection, to avoid inadvertent extravasation and its deleterious consequences, in particular with the two higher osmolar agents (gadopentetate dimeglumine and gadoversetamide)

Reviewer's Signature / Date: /S/	Team Leader's Signature / Date: /S/
Division Director Signature / Date: /S/	Office Director Signature / Date: /S/
Attachments:	

Cc: NDA #
HFD-XXX (Division File)/Requestor/
HFD-440 DD/TL/SE/Chron/Drug

Electronic File Name:

APPEARS THIS WAY
ON ORIGINAL

#3918245-3-00-01#

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291 Expires: 11/30/00
See OMB statement on reverse

Mfr report #: MK200111-0103 1

UF/Dist report #:

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier: [redacted] In confidence
2. Age at time of event: 76 or Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ____ (mo/day/yr)
   - [ ] life-threatening
   - [ ] hospitalization – initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other: ____
3. Date of event (mo/day/yr): 10/25/01
4. Date of this report (mo/day/yr): 11/8/01
5. Describe event or problem

Post injection, the patient became nauseated and vomited in the scanner.

[redacted]

No treatment. Patient recovered.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

JAN 1 4 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 OptiMARK 20mL Bottle
   #2
2. Dose, frequency & route used
   #1 40cc, IV
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1 MRA, subclavian
   #2
5. Event abated after use stopped or dose reduced
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
6. Lot # (if known)
   #1 C174M
   #2
7. Exp. date (if known)
   #1 JUN 03
   #2
8. Event reappeared after reintroduction
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
9. NDC # – for product problems only (if known)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - [ ] health professional
   - [ ] lay user/patient
   - [ ] other: ____
5. Expiration date (mo/day/yr)
6. model # ____
   catalog # ____
   serial # ____
   lot # ____
   other # ____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   [ ] yes [ ] no [ ] returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address: [redacted]
   phone #: [redacted]
2. Health professional? [X] yes [ ] no
3. Occupation: technologist
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

3918245-3-00-02

n of a report does not constitute on that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

(continued)
Refer to guidelines for specific instructions

FDA Use Only

F. For use by user facility/distributor–devices only

1. Check one: ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report: ☐ initial ☐ follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual): patient code ___ - ___ - ___; device code ___ - ___ - ___
11. Report sent to FDA? ☐ yes ____ (mo/day/yr) ☐ no
12. Location where event occurred: ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: ____ (specify) ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. Report sent to manufacturer? ☐ yes ____ (mo/day/yr) ☐ no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)

Mallinckrodt
675 McDonnell Blvd
PO Box 5840
St. Louis, MO 63134

2. Phone number: 314-654-2000
3. Report source (check all that apply): ☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☒ user facility ☐ company representative ☐ distributor ☐ other: ____
4. Date received by manufacturer (mo/day/yr): 11/08/01
5. (A)NDA # 20-937; IND # ____; PLA # ____; pre-1938 ☐ yes; OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply): ☐ 5-day ☐ 15-day ☐ 10-day ☒ periodic ☒ initial ☐ follow-up # ____
8. Adverse event term(s): nausea, vomiting
9. Mfr. report number: MK200111-0103 1

JAN 1 4 2002

H. Device manufacturers only

1. Type of reportable event: ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual): method ___ - ___ - ___ - ___; results ___ - ___ - ___ - ___; conclusions ___ - ___ - ___ - ___
7. If remedial action initiated, check type: ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/adjustment
8. Usage of device: ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data

e public reporting burden for this collection of information has been estimated to average one-ur per response, including the time for reviewing instructions, searching existing data sources, athering and maintaining the data needed, and completing and reviewing the collection of infor-ation. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

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U.S. Department of Health and Human Services

Individual Safety Report

4004402-7-00-01

For use by ~~user facilities~~, distributors and manufacturers for MANDATORY reporting

CDER

Page 1 of 2

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

Mfr report # ~~MK-200207-0097-1~~

Uf/Dist report # 180400

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: 30 or Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☒ other: Recovered

3. Date of event (mo/day/yr): 07-08-2002
4. Date of this report (mo/day/yr): 7-09-2002

5. Describe event or problem

Patient underwent a Head MRI/MRA for history of headaches. Procedure was at 2pm and he only had coffee all day. He was administered 19mL Optimark. Patient said he felt nauseated after needle was removed. After procedure was completed, patient sat up and he felt light-headed/whoozy, unsteady on his feet, clammy. Dr felt this was all due to vaso dilitation. He complained of increased salivation, itching on nose, and began shaking.

(continued on page 2)

6. Relevant tests/laboratory data, including dates

DSS NOV 06 2002

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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Penicillin allergy.
Had Omniscan two weeks before without incident.

DSS NOV 06 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 OPTIMARK 10X20 cc SYRINGE
#2

2. Dose, frequency & route used
#1 19 cc, IV, ONCE
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 7/8/02 - 7/8-02
#2

4. Diagnosis for use (indication)
#1 Head ache
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 D137E
#2

7. Exp. date (if known)
#1 05-2002
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # – for product problems only (if known)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
☐ health professional
☐ lay user/patient
☐ other:
5. Expiration date (mo/day/yr)
6. model # ____
catalog # ____
serial # ____
lot # ____
other # ____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address: [redacted] phone # [redacted]
2. Health professional? ☒ yes ☐ no
3. Occupation: Radiologist
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Individual Safety Report

4004402-7-00-02

Submission of a report does not constitute admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

180400

FDA Use Only

F. For use by user facility/distributor – devices only

1. Check one: ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report: ☐ initial ☐ follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual): patient code ___ - ___ - ___; device code ___ - ___ - ___
11. Report sent to FDA? ☐ yes ____ (mo/day/yr) ☐ no
12. Location where event occurred: ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: ____ (specify) ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. Report sent to manufacturer? ☐ yes ____ (mo/day/yr) ☐ no
14. Manufacturer name/address

DSS

NOV 0 6 2002

G. All manufacturers

1. Contact office – name/address (& mfrng site for devices)

Mallinckrodt, Inc
675 McDonnell Blvd
PO Box 5840
St Louis, MO 63134

2. Phone number: 314-654-2000
3. Report source (check all that apply): ☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☒ user facility ☐ company representative ☐ distributor ☐ other: ____
4. Date received by manufacturer (mo/day/yr): 07/09/2002
5. (A) NDA # 20-976; IND # ____; PLA # ____; pre-1938 ☐ yes; OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply): ☐ 5-day ☐ 15-day ☐ 10-day ☒ periodic ☒ initial ☐ follow-up # ____
8. Adverse event term(s): Nausea, Light-headed feeling, Saliva increased, pruritis, tremor, Vasodilitation, Headache, Hypoaesthesia
9. Mfr. report number: MK200207-0097-1

H. Device manufacturers only

1. Type of reportable event: ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual): method ___ - ___ - ___ - ___; results ___ - ___ - ___ - ___; conclusions ___ - ___ - ___ - ___
7. If remedial action initiated, check type: ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/adjustment
8. Usage of device: ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☒ Additional manufacturer narrative and/or 11. ☐ Corrected data

(continued from B.5.)
He stated he had a headache prior to the procedure which got worse. His BP was 140/90, pulse 80. He was sent to ER because radiologist was concerned shaking would develop into a seizure. He was put on a stretcher and developed a second episode of shaking, cold/clamminess. He remained lucid during incident.

Treatment: He was administered oxygen and transported to hospital where he was observed for several hours. He developed right-sided numbness while in ER.

The public reporting burden for this collection of information has been estimated to average one-half hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: DHHS Reports Clearance Office, Paperwork Reduction Project (0910-0291), Hubert H. Humphrey Building, Room 531-H, 200 Independence Avenue, S.W., Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

FDA Form 3500A - back

Individual Safety Report

#3918234-9-00-01#

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291 Expires: 11/30/00
See OMB statement on reverse

Mfr report # MK200111-0156 1

UF/Dist report #

FDA Use Only

USE BLACK INK

PLEASE TY

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: 58 or Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ____ (mo/day/yr)
   - [ ] life-threatening
   - [ ] hospitalization – initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other: ____
3. Date of event (mo/day/yr): 11/13/2001
4. Date of this report (mo/day/yr): 11/13/2001
5. Describe event or problem

Post injection for an MRI brain, the patient developed hives of the face, back and buttocks. Treatment 1 initiated. A Short time later, her voice became hoarse/raspy and she developed swelling around the eyes. Treatment 2 given. At the time the call was received, the patient's symptoms were improving.

Treatment 1: 25mg PO Valium, monitoring
Treatment 2: 25mg IV Benadryl, 125mg Solumedrol, IV fluids

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

JAN 1 4 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 OPTIMARK 20cc SYRINGE
   #2
2. Dose, frequency & route used
   #1 20cc, IV
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1 MRI, head
   #2
5. Event abated after use stopped or dose reduced
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
6. Lot # (if known)
   #1 C262B
   #2
7. Exp. date (if known)
   #1 SEP 03
   #2
8. Event reappeared after reintroduction
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
9. NDC # – for product problems only (if known)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - [ ] health professional
   - [ ] lay user/patient
   - [ ] other: ____
5. Expiration date (mo/day/yr)
6. model # ____
   catalog # ____
   serial # ____
   lot # ____
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   [ ] yes [ ] no [ ] returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
   phone #
2. Health professional? [X] yes [ ] no
3. Occupation: Chief Tech
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Medication and Device
Individual Safety Report

3918234-9-00-02

Submission of a report does not constitute
sion that medical personnel, user
tributor, manufacturer or product
d or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Use Only

For use by user facility/distributor—devices only

1. Check one
☐ user facility ☐ distributor

2. UF/Dist report number

3. User facility or distributor name/address

4. Contact person

5. Phone Number

6. Date user facility or distributor became aware of event (mo/day/yr)

7. Type of report
☐ initial
☐ follow-up # ____

8. Date of this report (mo/day/yr)

9. Approximate age of device

10. Event problem codes (refer to coding manual)
patient code ____ - ____ - ____
device code ____ - ____ - ____

11. Report sent to FDA?
☐ yes _____ (mo/day/yr)
☐ no

12. Location where event occurred
☐ hospital
☐ home
☐ nursing home
☐ outpatient treatment facility
☐ outpatient diagnostic facility
☐ ambulatory surgical facility
☐ other: _____ specify

13. Report sent to manufacturer?
☐ yes _____ (mo/day/yr)
☐ no

14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)
Mallinckrodt
675 McDonnell Blvd.
PO Box 5840
St. Louis, MO 63134

2. Phone number
314-654-2000

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☒ user facility
☐ company representative
☐ distributor
☐ other: _____

4. Date received by manufacturer (mo/day/yr)
11/13/01

5. (A)NDA # 20-976
IND # _____
PLA # _____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ initial ☐ follow-up # ____

8. Adverse event term(s)
Urticaria, hoarseness, oedema periorbital

9. Mfr. report number
MK200111-0156 1

H. Device manufacturers only

1. Type of reportable event
☐ death
☐ serious injury
☐ malfunction (see guidelines)
☐ other: _____

2. If follow-up, what type?
☐ correction
☐ additional information
☐ response to FDA request
☐ device evaluation

3. Device evaluated by mfr?
☐ not returned to mfr.
☐ yes ☐ evaluation summary attached
☐ no (attach page to explain why not) or provide code: _____

4. Device manufacture date (mo/yr)

5. Labeled for single use?
☐ yes ☐ no

6. Evaluation codes (refer to coding manual)
method ____ - ____ - ____ - ____
results ____ - ____ - ____ - ____
conclusions ____ - ____ - ____ - ____

7. If remedial action initiated, check type
☐ recall
☐ repair
☐ replace
☐ relabeling
☐ other: _____
☐ notification
☐ inspection
☐ patient monitoring
☐ modification/adjustment

8. Usage of device
☐ initial use of device
☐ reuse
☐ unknown

9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:

10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data

JAN 1 4 2002

ublic reporting burden for this collection of information has been estimated to average one- per response, including the time for reviewing instructions, searching existing data sources, thering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

391B248-9-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, butors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291 Expires: 11/30/00
See OMB statement on reverse

Mfr report #: MK200110-0012 1
UF/Dist report #:
FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: 40 or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   ☐ death (mo/day/yr)
   ☐ life-threatening
   ☐ hospitalization – initial or prolonged
   ☐ disability
   ☐ congenital anomaly
   ☐ required intervention to prevent permanent impairment/damage
   ☐ other:
3. Date of event (mo/day/yr): 10/01/01
4. Date of this report (mo/day/yr): 10/02/01
5. Describe event or problem

Two hours after hand injection of 20 mL OptiMARK yesterday evening, the patient developed a large hot spot at the injection site and hives on her arms. Patient took 2 Benadryl PO. The hives spread to her chest, neck and buttocks. Patient took a third Benadryl during the night. Symptoms were improving by the morning.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

JAN 1 4 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 OptiMARK 20mL Bottle
   #2
2. Dose, frequency & route used
   #1 20cc, IV
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1 MRI
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 C053M
   #2
7. Exp. date (if known)
   #1 FEB 03
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   ☐ health professional
   ☐ lay user/patient
   ☐ other:
5. Expiration date (mo/day/yr)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
   phone #
2. Health professional? ☒ yes ☐ no
3. Occupation: technologist
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

PLEASE USE BLACK INK

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

3916248-9-00-02

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that medical personnel, user
facility, distributor, manufacturer or product
caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

(continued)
Refer to guidelines for specific instructions

FDA Use Only

F. For use by user facility/distributor–devices only

1. Check one: ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report: ☐ initial ☐ follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual)
patient code ___ - ___ - ___
device code ___ - ___ - ___
11. Report sent to FDA? ☐ yes ____ (mo/day/yr) ☐ no
12. Location where event occurred: ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: ____ specify ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. Report sent to manufacturer? ☐ yes ____ (mo/day/yr) ☐ no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfrng site for devices)

Mallinckrodt
675 McDonnell Blvd
PO Box 5840
St. Louis, MO 63134

2. Phone number: 314-654-2000
3. Report source (check all that apply): ☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☒ user facility ☐ company representative ☐ distributor ☐ other: ____
4. Date received by manufacturer (mo/day/yr): 10/02/01
5. (A)NDA # 20-937 IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply): ☐ 5-day ☐ 15-day ☐ 10-day ☒ periodic ☒ initial ☐ follow-up # ____
8. Adverse event term(s)

urticaria,
injection site reaction

JAN 1 4 2002

9. Mfr. report number: MK200110-0012 1

H. Device manufacturers only

1. Type of reportable event: ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual)
method ___ - ___ - ___ - ___
results ___ - ___ - ___ - ___
conclusions ___ - ___ - ___ - ___
7. If remedial action initiated, check type: ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/adjustment
8. Usage of device: ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data

public reporting burden for this collection of information has been estimated to average one-
per response, including the time for reviewing instructions, searching existing data sources,
ering and maintaining the data needed, and completing and reviewing the collection of infor-
tion. Send comments regarding this burden estimate or any other aspect of this collection of
information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

Individual Safety Report

#3684222-3-00-01#

[redacted] MEDICAL

MEDWATCH

Approved by FDA 05/12/94

Mfr Report # 15412-01M/3053

UF/Dist report #

FDA Use Only

Patient information

1. Patient Identifier	2. Age at time of event:	3. Sex	4. Weight
UNKNOWN In confidence	38 or Date of Birth:	[X] female [ ] male	___ lbs or ___ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ___ (day/mo/yr)
   - [X] life-threatening
   - [ ] hospitalization - initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other: ___

3. Date of event (day/mo/yr): 13-MAR-2001

4. Date of this report (day/mo/yr): 14-MAR-2001

5. Describe event or problem

PATIENTS HAD A SEIZURE CONSISTING OF HER EYES ROLLING BACK IN HER HEAD AND TAUTNESS OF THE EYELIDS AFTER INJECTION OF 4 ML WHICH APPEARED TO BE EXTRAVASATED. PATIENT STOPPED BREATHING AND HAD NO PULSE. CPR WAS DONE WHICH WAS SUCCESSFUL. PATIENT TRANSPORTED TO HOSPITAL ER AND WAS CONSCIOUS WHEN LEFT CLINIC. REPORTER THOUGHT SYMPTOMS COULD BE ANXIETY-REALTED.

(EE CHEST COMPRESSIONS

MAR 19 2001 CDER EVALUATION AND RESEARCH

6. Relevant tests/laboratory data, including dates

MAR 19 2001

7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

PATIENT HAS M.S.

DSS

MAR 20 2001

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 OPTIMARK (PLASTIC)
   - #2

2. Dose, frequency & route used
   - #1 4 ML INTRAVENOUS
   - #2

3. Therapy dates (if unknown, give duration from/to (or best estimate))
   - #1 13-MAR-2001
   - #2

4. Diagnosis for use (indication)
   - #1 MRI HEAD
   - #2

5. Event abated after use stopped or dose reduced
   - #1 [ ] yes [ ] no [ ] doesn't apply
   - #2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
   - #1 B340 A
   - #2

7. Exp. date (if known)
   - #1
   - #2

8. Event reappeared after reintroduction
   - #1 [ ] yes [ ] no [ ] doesn't apply
   - #2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

UNKNOWN

G. All manufacturers

1. Contact office - name/address

MALLINCKRODT INC.
P.O. BOX 5840
ST. LOUIS, MO 63134

2. Phone number: (314) 654 - 2000

3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [ ] consumer
   - [X] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:

4. Date received by manufacturer (day/mo/yr): 14-MAR-2001

5. (A)NDA # 20-976
   - IND # ___
   - PLA # ___
   - pre-1938 [ ] yes
   - OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
   - [ ] 5-day [X] 15-day
   - [ ] 10-day [ ] periodic
   - [X] initial [ ] follow-up #

8. Adverse event term(s)
   - CARDIAC ARREST
   - RESPIRATORY ARREST
   - UNCONSCIOUSNESS

9. Mfr. report number: 15412-01M/3053

E. Initial reporter

1. Name, address & phone #

Phone: [redacted]

2. Health professional: [X] yes [ ] no

3. Occupation

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [ ] unk

FACSIMILE

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Individual Safety Report
3911731-1-00-01

MEDWATCH
FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

MAY 0 3 2002

Page 1 of 2

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

Mfr report #: MK200205-0021-1
UF/Dist report #:
FDA Use Only

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: 52 or Date of birth:
3. Sex: ☐ female ☑ male
4. Weight: 0 lbs or ___ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☑ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 4/30/02
4. Date of this report (mo/day/yr): 5/1/02
5. Describe event or problem

AE
52 YEAR OLD MALE PATIENT HAVING A LUMBAR MRI FOR POST SURGICAL FOLLOW UP, BEGAN SWEATING, DEVELOPED CONVULSIONS (ARCHING OF UPPER BACK WITH RIGIDITY), LOST BODILY FUNCTIONS (URINATED), HAD DECREASED BLOOD PRESSURE, HIS EYES ROLLED BACK AND HE LOST CONSCIOUSNESS. WHEN HE RECOVERED CONSCIOUSNESS, HE REPORTED HE HAD NOTICED A METALLIC TASTE AND A BURNING PAIN IN HIS ARM DURING THE INJECTION. DOSE WAS 13 ML AND INJECTION WAS DONE IN HAND.

TIENT WAS INTUBATED AND SENT TO ICU. PATIENT IS ILL HOSPITALIZED ON 5/1/02 BUT IS DOING BETTER AND ASKING FOR FOOD. MAY BE SENT TO A PRIVATE ROOM ON 5/1/02.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

PLEASE TYPE OR USE BLACK INK

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 OPTIMARK 10X20CC SYR
   #2
2. Dose, frequency & route used
   #1 13 ML, IV, ONCE
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 04/30/02-04/30/02
   #2
4. Diagnosis for use (indication)
   #1 LUMBAR MRI
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 D041C
   #2
7. Exp. date (if known)
   #1 FEB 04
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☑ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model #
   catalog # 117720
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☑ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

DSS
MAY 0 6 2002

E. Initial reporter

1. Name & address
   phone #
2. Health professional? ☑ yes ☐ no
3. Occupation: RT
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☑ unk

FDA Form 3500A

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MAY 0 3 2002

Individual Safety Report

3911731-1-00-02

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caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service · Food and Drug Administration

er to guidelines for specific instructions

FDA Use Only

F. For use by user facility/distributor–devices only

1. Check one
   - [ ] user facility
   - [ ] distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report
   - [ ] initial
   - [ ] follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual)
    - patient code ___ - ___ - ___
    - device code ___ - ___ - ___
11. Report sent to FDA?
    - [ ] yes ____ (mo/day/yr)
    - [ ] no
12. Location where event occurred
    - [ ] hospital
    - [ ] home
    - [ ] nursing home
    - [ ] outpatient treatment facility
    - [ ] other: ____ specify
    - [ ] outpatient diagnostic facility
    - [ ] ambulatory surgical facility
13. Report sent to manufacturer?
    - [ ] yes ____ (mo/day/yr)
    - [ ] no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)

   MALLINCKRODT INC
   675 MCDONNELL BLVD
   PO BOX 5840
   ST LOUIS MO 63134

2. Phone number: 314 654 2000
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [ ] consumer
   - [x] health professional
   - [x] user facility
   - [x] company representative
   - [ ] distributor
   - [ ] other: ____
4. Date received by manufacturer (mo/day/yr): 4/30/02
5. (A)NDA # 20-976
   - IND # ____
   - PLA # ____
   - pre-1938 [ ] yes
   - OTC product [ ] yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - [ ] 5-day
   - [x] 15-day
   - [ ] 10-day
   - [ ] periodic
   - [x] initial
   - [ ] follow-up # ____
8. Adverse event term(s)

   DIAPHORESIS, PAIN, TASTE PERVERSION, CONVULSIONS, HYPOTENSION, URINARY INCONTINENCE UNCONSCIOUSNESS

9. Mfr. report number: MK200205-0021-1

H. Device manufacturers only

1. Type of reportable event
   - [ ] death
   - [ ] serious injury
   - [ ] malfunction (see guidelines)
   - [ ] other: ____
2. If follow-up, what type?
   - [ ] correction
   - [ ] additional information
   - [ ] response to FDA request
   - [ ] device evaluation
3. Device evaluated by mfr?
   - [ ] not returned to mfr.
   - [ ] yes [ ] evaluation summary attached
   - [ ] no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use?
   - [ ] yes [ ] no
6. Evaluation codes (refer to coding manual)
   - method ___ - ___ - ___ - ___
   - results ___ - ___ - ___ - ___
   - conclusions ___ - ___ - ___ - ___
7. If remedial action initiated, check type
   - [ ] recall
   - [ ] repair
   - [ ] replace
   - [ ] relabeling
   - [ ] other: ____
   - [ ] notification
   - [ ] inspection
   - [ ] patient monitoring
   - [ ] modification/adjustment
8. Usage of device
   - [ ] initial use of device
   - [ ] reuse
   - [ ] unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. [ ] Additional manufacturer narrative and/or 11. [ ] Corrected data

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MAY 0 6 2002

MDR Mail Date: ____

Public reporting burden for this collection of information has been estimated to average one-hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

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4022509-5-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

y user-facilities
d manufacturers for
TORY reporting

RECEIVED DEC 0 6 2002

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

Mfr report # MK200205-0021-1

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: 52 or Date of birth:
3. Sex: ☐ female ☑ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☑ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 4/30/02
4. Date of this report (mo/day/yr): 12/5/02
5. Describe event or problem

52 YEAR OLD MALE PATIENT HAVING A LUMBAR MRI FOR POST SURGICAL FOLLOW UP, BEGAN SWEATING, DEVELOPED CONVULSIONS (ARCHING OF UPPER BACK WITH RIGIDITY), LOST BODILY FUNCTIONS (URINATED),HAD DECREASED BLOOD PRESSURE, HIS EYES ROLLED BACK AND HE LOST CONSCIOUSNESS. WHEN HE RECOVERED CONSCIOUSNESS, HE REPORTED HE HAD NOTICED A METALLIC TASTE AND A BURNING PAIN IN HIS ARM DURING THE INJECTION. DOSE WAS 13 ML AND INJECTION WAS DONE IN HAND.

PATIENT WAS INTUBATED AND SENT TO ICU. PATIENT IS TILL HOSPITALIZED ON 5/1/02 BUT IS DOING BETTER ND ASKING FOR FOOD. MAY BE SENT TO A PRIVATE ROOM ON 5/1/02.

Addendum 12/2/02: CPM contacted ... [redacted] for an update to the patient outcome. She stated that the patient was discharged from the hospital within a couple days of the event without any residual symptoms. Completely recovered to the best of her knowledge.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

USE BLACK INK

PLEASE TY

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 OptiMARK 10x20cc syringe
   #2
2. Dose, frequency & route used
   #1 13 mL, IV, once
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 04/30/02-04/30/02
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 D041C
   #2
7. Exp. date (if known)
   #1 FEB 04
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☑ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
   phone #: [redacted]
2. Health professional? ☑ yes ☐ no
3. Occupation: RT
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☑ unk

DEC 0 6 2002

DS

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

FDA Form 3500A

DEC 0 9 2002

Medic
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4022509-5-00-02

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Use Only

F. For use by user facility/distributor–devices only

1. Check one: ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report: ☐ initial ☐ follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual)
patient code ___ - ___ - ___
device code ___ - ___ - ___
11. Report sent to FDA? ☐ yes ____ (mo/day/yr) ☐ no
12. Location where event occurred: ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ outpatient diagnostic facility ☐ ambulatory surgical facility ☐ other: ____ specify
13. Report sent to manufacturer? ☐ yes ____ (mo/day/yr) ☐ no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)
MALLINCKRODT
675 MCDONNELL BLVD
PO BOX 5840
ST LOUIS MO 63134
2. Phone number: 314 654 2000
3. Report source (check all that apply): ☐ foreign ☐ study ☐ literature ☐ consumer ☑ health professional ☑ user facility ☑ company representative ☐ distributor ☐ other:
4. Date received by manufacturer (mo/day/yr): 12/2/02
5. (A)NDA # 20-976
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply): ☐ 5-day ☑ 15-day ☐ 10-day ☐ periodic ☐ Initial ☑ follow-up # 01
8. Adverse event term(s)
DIAPHORESIS, PAIN, TASTE PERVERSION, CONVULSIONS, HYPOTENSION, URINARY INCONTINENCE, UNCONSCIOUSNESS
9. Mfr. report number
MK200205-0021-X

H. Device manufacturers only

1. Type of reportable event: ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual)
method ___ - ___ - ___ - ___
results ___ - ___ - ___ - ___
conclusions ___ - ___ - ___ - ___
7. If remedial action initiated, check type: ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/adjustment
8. Usage of device: ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data

MDR Mail Date: ____

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FDA Form 3500A - back

DEC 06 2002

DEC 09 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

PRIOR APPROVAL SUPPLEMENT

Mallinckrodt Inc.
Attention: Mr. Edward R. Porter
Manager Regulatory Affairs
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Dear Mr. Porter:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
20-937	S-003	Optimark® (gadoversetamide injection)
20-975	S-003	Optimark® (gadoversetamide injection) Pharmacy Bulk Pack
20-976	S-003	Optimark® (gadoversetamide injection) Plastic Syringe

Date of Supplements: March 29, 2002

Date of Receipt: April 1, 2002

These supplements provide safety data supporting the safe administration of Optimark® with a power injector which may support revisions to the product labeling, specifically removal of the statement "Has not been evaluated for drug delivery by a power injector."

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on June 1, 2002, in accordance with 21 CFR 314.101(a). If the applications are filed, the primary user fee goal date will be February 1, 2003, and the secondary user fee goal date will be April 1, 2003.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Tia Harper-Velazquez, Pharm.D., Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Kyong Cho, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research