Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-976 SUPPL #_____
Trade Name: Optimark **Generic Name: Gadoversetamide**
Applicant Name: Mallinckrodt **HFD # 160**
Approval Date If Known: December 8, 1999

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /x/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /x/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /x/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA 20-976

Division File NDA 20-976

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE
SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /x/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: *Title:* Project Manager *Date:* 11-6-99

Signature of Office/Division Director

Signature: *Date:* 11-29-99

cc: *Original NDA 20-976*
Division File 20-976
HFD-93 Mary Ann Holovac

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-937 SUPPL #_____
Trade Name: Optimark **Generic Name: Gadoversetamide**
Applicant Name: Mallinckrodt **HFD # 160**
Approval Date If Known: December 8, 1999

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /x/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /x/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /x/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 8/27/97
cc: Original NDA 20-937

Division File NDA 20-937

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? **(Rx to OTC switches should be answered NO - please indicate as such)**

YES /___/ NO /x/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: [signature] *Date:* 11-6-99
Title: Project Manager

Signature of Office/Division Director
Signature: [signature] *Date:* 11-29-99

cc: *Original NDA 20-937*
Division File 20-937
HFD-93 Mary Ann Holovac

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-975 SUPPL #_____
Trade Name: Optimark Generic Name: Gadoversetamide
Applicant Name: Mallinckrodt HFD # 160
Approval Date If Known: December 8, 1999

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /x/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /x/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /x/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 8/27/97
cc: Original NDA 20-975

Division File NDA 20-975

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE
SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /x/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: [signature] *Date:* 11-6-99
Title: Project Manager

Signature of Office/Division Director
Signature: [signature] *Date:* 11-29-99

cc: *Original NDA 20-975*
Division File 20-975
HFD-93 Mary Ann Holovac

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From:	**Division of Medical Imaging and Radiopharmaceutical Drug Products**	**HFD-160**
	Attention: David A. Place, PhD	**Phone:** (301) 443-1560

Date: 7/20/98

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: OptiMARK	**NDA# 20-937** (Individual vials) **20-975** (Pharmacy Bulk Pack) **20-976** (Single Use Prefilled Syringes)

Established name, including dosage form:
gadoversetamide solution for IV injection

Other trademarks by the same firm for companion products:
The other MRI contrast agent that Mallinckrodt manufactures and distributes is GastroMARK (ferumoxsil suspension) for the sponsor Advanced Magnetics, Inc. (NDA # 20-410).

Indications for Use (may be a summary if proposed statement is lengthy):
MRI agent for central nervous system and liver.

Initial Comments from the submitter (concerns, observations, etc.):
No concerns

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

DIVISION DIRECTOR MEMO TO THE FILE

NDA:	20-937 (Parent NDA in Glass Vials) 20-975 (Pharmacy Bulk Pack) 20-976 (Plastic Syringes)
DRUG:	OptiMark (Gadoversetamide) Injection
CLASS:	Gadolinium Contrast Agent
ROUTE:	Intravenous Injection
INDICATION:	Contrast Enhancement in CNS and Liver
MODALITY:	MRI (Magnetic Resonance Imaging)
CATEGORY:	1S – Resubmission – Response to Nonapprovable Action
SPONSOR:	Mallinckrodt, Inc.
SUBMITTED:	June 08, 1999
PDUFA:	December 08, 1999
COMPLETED:	November 26, 1999

12/08/99

RELATED REVIEWS:

Division Summary 12/10/98
Chemistry - D. Place, Ph.D; 12/08/98, 11/07/99 (3 reviews, one/NDA)
Clinical - R. Raman, M.D.; 12/04/98, 11/26/99; E. Jones, 12/04/98
Microbiology - B Uratani, Ph.D.; 4/24/98
Pharmacokinetics - YM Choi, Ph.D; 11/03/98
Pharmacology - J Melograna, MS; 12/03/98
Statistics - R. Davi, Ph.D.; 11/06/98, 11/18/99
Project Manager - J. Moore, RPh

RELATED DRUGS: Magnevist, Omniscan, and Prohance
All three are gadolinium based contrast agents approved for intravenous injection at 0.1 mmol/kg. Two are approved for a repeat 0.2 mmol/kg injections.

BACKGROUND:

OptiMark (gadoversetamide) Injection was developed by Mallinckrodt, Inc. as a contrast agent to enhance Magnetic Resonance Imaging. The original NDA was submitted in March 02, 1998 and was found to be deficient in chemistry and clinical safety assessments. A non-approval letter issued on December 23, 1999. The application was resubmitted June 08, 1999 and is now approvable with labeling revisions, safety clarifications, and a phase 4 commitment.

Magnetic Resonance Imaging (MRI) reflects proton alignment within a magnetic field by detecting differences in proton density, changes in longitudinal (T1) and transverse (T2) relaxation time. When drugs that interact with the magnetic field are introduced, they can affect the T1 and/or the T2 relaxation times and thus change the detect contrast (signal intensity) within an organ or tissue. OptiMark is intended to primarily affect T1 imaging and has been developed for the following proposed indications:

> *"OptiMark injection is indicated for use with MRI in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood brain barrier. OptiMark injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.*
>
> *"..... for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues*
>
> *..... for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions in the liver"*

All discipline reviews are complete and recommend approval or approvable with labeling revisions. During the first review cycle, the microbiology, pharmocology-toxicology, and pharmacokinetic-pharmacodynamic portions of the application were acceptable for approval with labeling revisions. During this review cycle the chemistry and clinical portions were found to be acceptable. This memorandum will concentrate on the resolution of the summary deficiencies noted in my memorandum to the file dated December 10, 1999.

As noted in the original division summary, currently 3 gadolinium based drugs are marketed in the US for contrast enhancement in MRI. These are Magnevist, OmniScan and ProHance. Their approved indications and doses are similar and are summarized in table 1. All are marketed in glass vials. Omniscan and ProHance also are in plastic syringes. To date, none of these are available in a pharmacy bulk package. The first two proposed indications listed on the preceding page for OptiMark (intracranial lesions, and spine and associated tissues) are similar to the labeling of the other approved gadolinium agents. However, none of the other gadolinium agents have a specific liver indication. The closest other indication is for the "body" defined as intrathoracic (excluding) the heart and intraabdominal regions. The dose proposed for OptiMark (0.1 mmol/kg) is the standard, lowest dose approved. The proposed OptiMark pharmacy bulk package would be supplied as a 50 mL vial.

Table I. Indication Comparison with Approved MRI Contrast Drugs							
Drug	CNS	Spine &	Body[(b)]	Head		Dose (mmol/kg)	
						0.1	0.2 [(c)]
Magnevist	x	x	x	x		x [(d)]	
OmniScan	x	x	x			x	x [(e)]
ProHance	x			x		x	x
OptiMark	x	x			x	x	

(a) Adults and pediatrics over 2 years
(b) Body is considered to be intrathoracic (excluding the heart) and intraabdominal regions
(c) As a second dose if needed for MRI of CNS
(d) Has upper limit of 20 mL
(e) Dosing chart highest total volume = 18 mL; also approved for bolus injection

CHEMISTRY

OptiMark (gadoversetamide) for Injection is a non-ionic gadolinium chelated of diethylenetriamine pentaacetic acid bismethoxyethylamide. Its chemical name is [8,11-bis(carboximethyl)-14[2-[2-methoxethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)] gadolinium. The molecular formula is $C_{20}GdH_{34}N_5O_{10}$; the molecular weight is 661.77 g/mol.

During the first review cycle, Dr. Place's review notes that the application lacked data on a critical component, calcium versetamide. Versetamide is the ligand that binds gadolinium and can bind to other anions. The sponsor notes that free versetamide is included in the final product to "stabilize" the gadoversetamide. However, as noted by Dr. Place, when calcium hydroxide and calcium dihydrate are added during manufacturing, the calcium exchanges with versetamide and forms calcium versetamide. This results in an agent with both gadoversetamide and calcium versetamide (as well as free gadolinium). To resolve this deficiency, data were requested on the "1) manufacturing process and full characterization of calversetamide reference standard, 2) modification of all labeling to reflect the actual chemical composition of the drug product, 3) revision of the drug product specifications, revision of the manufacturing instructions and associated documentation to incorporate controls that assay for calversetamide, and 4) establishment and validation of regulatory methods that determine calversetamide

content and limits at time of manufacture and over the proposed expiry period. These data were supplied and found to be acceptable. In addition, the sponsor responded adequately to deficiencies on the pharmacy bulk package and the plastic syringe (Ultrajet).

During the original review cycle an inspection resulted in the issuance of a Warning letter because of major plant deficiencies that would affect the product line. Reinspection was found to be acceptable in December, 1998.

Environmental Assessment: A categorical exclusion waiver was accepted on the first review cycle.

Labeling: Minor revisions were recommended by Dr. Place and are included in the FDA revisions.

MICROBIOLOGY: Recommended approval during the first review cycle.

PHARMACOLOGY-TOXICOLOGY: Recommended approval with labeling revisions during the first review cycle.

CLINICAL PHARMACOLOGY: During the first review cycle, the clinical pharmacology section was recommended for approval with labeling revisions. Also requested was confirmation of a non-compartment model and renal clearance completed by the clinical pharmacology reviewer. These data were submitted and found to be acceptable by Dr. Sancho. The information is included in the revised labeling.

CLINICAL

A. Efficacy:

The use of OptiMark for CNS and Liver imaging was found to be acceptable during the first review cycle; however, the sponsor was asked to verify the FDA statistical analysis and representation of the data. Specifically, CNS and liver studies evaluated enriched populations of patients who had an abnormality on baseline CT or MRI and were highly suspect for disease. The protocol endpoints included: confidence in the diagnosis, conspicuity of all lesions, delineation of lesion borders, the number of lesions, confidence in the number of lesions, distinction of edema from pathology, effect on the next management step, and the proportion of lesions that were not visualized. The trial design did not include a rigorous confirmation of the final diagnosis. that edematous lesions were not pathologic, or that the effect on the next management step was appropriate. Therefore, these measures were considered as

supportive but not definitive. Therefore, the decision to approve is based on the more objective endpoints. Also, the sponsor's analytic plan was based on the differences of the means using a unconventional mathematical formula. Comparability between OptiMark and the control agent was proposed as formula results values that ranged between 1.5 to –1.5. The clinical relevance of this formula and these numbers were not established in the NDA. Therefore, the reviewing statistician analyzed the data with a more traditional approach (e.g., for each endpoint, the number of images that were the same, better or worse). The action letter requested confirmation of this analysis. These data were included in the resubmission and were found to be acceptable. Two summary tables of these data are derived from Dr. Davi's review and reproduced from my memorandum of December 10, 1998 and are attached to pages 13-14. These form the basis of the FDA draft labeling revisions. Note that the attached summary tables show a comparison between OptiMark and Magnevist. However, the data are derived from parallel patients, not cross over patients. Also, the statistical analysis is not considered sufficient to confirm equivalence of the two drugs. Additionally, as noted during the first review cycle, Magnevist does not have a specific liver indication. Hence, the Magnevist data were considered supportive. Therefore, the labeling presents the data from OptiMark in reference to the baseline noncontrast MRIs, only.

Indications: Mallinkcrodt submitted proposed labeling language that is a composite between the labels of Magnevist, OmniScan and ProHance. Upon review, the CNS indication in the FDA revision reflects the language in the two most recently approved drugs (OmniScan and ProHance). The liver indication is unique to OptiMark and reflects the studied population.

B. Safety:

The outstanding safety concern from the first review cycle was the limited ability to evaluate the ECG data and the potential relationship of any QTc abnormality to the gadolinium-calcium versetamide chemistry questions. Specifically, recent literature suggests that gadolinium may block the calcium channel. (See Dr. Raman's memorandum of 11/29/99). If a drug alters ventricular repolarization, it may increase the risk of developing a malignant arrhythmia. QT interval prolongation is a measure of the ventricular repolarization. However, the threshold or amount of prolongation at which risk begins or does not exist is not established. Also, not known is the relationship of the frequency of observed prolongations to the risk of malignant arrhythmia in a larger treated population. Measured QT intervals vary with the heart rate and the implications of a given number are greater when the heart rate is considered. QT interval prolongation is generally adjusted for the heart rate. These adjustments are known as the corrected QT (i.e., QTc Interval). A commonly accepted method is the Bazett's formula [QTc = QT/SQRT(RR)]. The action letter requested a detailed analysis of the patients who had frequent ECG measurements and the use of generally accepted definitions of ECG interval abnormalities. These data were submitted and reviewed by Dr. Raman. His review notes that the database is still limited in scope; however, it is acceptable for labeling. The specifics are summarized below.

Overall, 1663 patients were exposed to at least one dose of OptiMark. Of these approximately 387 had ECGs at 1 hour and 24 hours after injection. Of the 387 patients, 175 had ECGs more frequently monitored (i.e., immediately and at 15, 30, 60, 120 minutes and 24 hours after injection). These patients were in two dose finding studies (# 489 and #538). The data were analyzed by the number of patients who had QTc interval prolongation of <30, 30-60, and >60 mseconds. The upper limit of normal intervals for the reanalysis is 425 mseconds.

Dr. Raman's review presents the data analysis for the number of patients with QT or QTc prolongation at different time points and concentrates on the two studies with frequent early time point monitoring. Additionally, his review tables are supplemented with patients from other studies that happened to have data at a specific time point (i.e., 1 hour or 24 hours). This provides the largest number of patients who have evaluable data at any time point.

In order to gain a perspective of the 175 patients with frequently repeated monitoring, the following table 2 presents a synthesis of Dr. Raman's tables and focuses on the QTc prolongation only. This table includes information on the placebo treated patients (derived from the sponsor's volume 11.010). This table presents the data only from those patients who had monitoring immediately through 24 hours. The first

column of table 2 provides the dose of OptiMark or Placebo (and the number of patients in the dosing group). The second column presents the time points monitored and the number of available ECGs at those time points. The third column is the number of patients who had QTc interval prolongation of less than 30 milliseconds. The forth column is the number with QTc prolongation greater than 30 mseconds up to 60 mseconds; and the fifth column is the number of patients with QTc prolongation greater than 60 mseconds.

As shown in the table, each of the 175 frequently monitored patients, regardless of OptiMark dose or placebo, had some type of QTc prolongation event. The differences are in the magnitude of the prolongation. When considering the dose, in the patients who received the proposed for market 0.1 mmol/kg dose, the majority 87 to 92/93 (96 -99%) had QTc prolongation values that were less than 30 mseconds at some monitoring time point. Of these 92 patients, 72 (78%) had prolongations that were less than 5 mseconds. Also, 2 patients had prolongation between 25 to 30 msec category; i.e., these 2 patients approached the categorical threshold of 30 mseconds.

Overall all time points, of the 93 monitored patients who received 0.1 mmol/kg, 15 (16%) had QTc prolongation of >30- <60 mseconds, and 4 (4%) had > 60 msecond changes. On pages 12-16 of his review, Dr. Raman summarizes the associated abnormalities in those patients who received 0.1 mmol/kg and had > 61 msecond prolongation (page 12 and 15) and any change over 30 mseconds (page 13). In 3 of these 4 patients, the prolongation was noted at 24 hours and was in the absence of other clinical findings, metabolic abnormalities, hemodynamic abnormality, or cardiac disease history. In the forth patient, the prolongation occurred one hour after injection and the patient had nausea and headache.

The data were considered for possible dose response effects. Given the sample size, one patient causes a 2.3% difference. When looking at the percent of patients with QTc prolongation of >30-60 mseconds and >60 mseconds except for the percentage of patients at the "immediate" time point, the frequencies are similar. At the immediate time point, the placebo group and 0.5 mmol/kg group had the highest frequencies of 7 % and 7.9 %, respectively. Overall, the sample sizes are probably too small to support a definitive assessment of dose response.

Table 2: (Study # 489 and #538) Number of Patients with QTc Prolongation[a] at Early Time Point Monitoring				
Dose	Time Points Monitored [b]	≤30 mseconds	>30-60 msec	>60 msec
0.1 mmol/kg (N = 93)	Immediate (N= 92)	92 (100%)	0	0
	15 minutes (n= 92)	91 (99%)	1 (1%)	0
	30 minutes (=93)	92 (99%)	1 (1%)	0
	1 hr (n= 93)	87 (96%)	4 (4%)	2 (2%)
	2 hr (n =93)	89 (96%)	4 (4%)	0
	24 hr (n = 91)	87 (96%)	3 (3%)	1 (1%)
0.3mmol/kg (N = 42)	Immediate	39 (95%)	2 (5%)	0
	15 minutes (n= 41)	41 (100%)	0	0
	30 minutes (=42)	42 (100%)	0	0
	1 hr (n=42)	40 (95%)	2 (5%)	0
	2 hr (n =42)	42 (100%)	0	0
	24 hr (n = 42)	42 (100%)	0	0
0.5 mmol/kg (N = 41)	Immediate (N= 38)	34 (89%)	3 (7.9%)	1 (2.6%)
	15 minutes (n= 38)	37 (97%)	1 (2.6%)	0
	30 minutes (=38)	37 (97%)	1 (2.6%)	0
	1 hr (n=38)	38 (100%)	0	0
	2 hr (n =38)	38 (100%)	0	0
	24 hr (n = 38)	36 (94%)	2 (5.3%)	0
Placebo (c) (N= 42)	Immediate (n=41)	41 (100%)	0	0
	15 minutes (n= 38)	38 (100%)	3 (7%)	1 (2%)
	30 minutes (=41)	41 (100%)	1 (2%)	0
	1 hr (n=41)	41 (100%)	1 (2%)	0
	2 hr (n =41)	38 (93%)	2 (5%)	1 (2%)
	24 hr (n = 42)	41 (98%)	1 (2%)	0

(a) Bazett's Formula correction
(b) The number of patients at each time point may be the same or different patients. The numbers cannot be added
(c) From volume 11, page 010 (not in Raman's review)

Of the remaining patients who had ECGs monitored at 1 hour or at 24 hours, the following are noted. Eight (8) additional patients had ECGs at 1 hour and 294 had ECGs at 24 hours. Their interval groups are shown in table 3 in comparison to the

frequently monitored patients. (For ease of comparison, these numbers are reproduced from the preceding table.) Also, the separate control group of patients who received Magnevist also had ECGs at 24 hours only. Their data are reflected in the last row of this table. As can been seen in the table, the percentages of QTc prolongation at 24 hours are similar in the frequently and infrequently monitored patients who received OptiMark and in the patients who received Magnevist. The number of additional patients who received monitoring at 1 hour are too small to support a comparison

Table 3:
Number of Patients with QTc Prolongation(a) at Early Time Point Monitoring

OptiMark = 0.1 mmol/kg	<30 msec	30-60 msec	>60 msec
1 Hour			
Frequently monitored (n=93)	87 (96%)	4 (4%)	2 (2%)
Infrequently monitored (n=8)	6 (75%)	0	0
24 Hours			
Frequently monitored (n=93)	87 (96%)	3 (3%)	1 (1%)
Infrequently monitored (n=294)	283 (96%)	12 (4%)	1 (0.03%)
Magnevist = 0.1 mmol/kg			
Frequently Monitored (N = 0)	n.a.	n.a.	n.a.
24 hours - Infrequently Monitored (N=214)	206 (96%)	7 (3%)	1 (0.5%)

Other ECG intervals: Dr. Raman's review analyzed the PT, QRS, T/U wave intervals. Each individual interval is summarized on pages 16-18 of his review. The combined set is summarized on page 19 and reveals that one patient had abnormalities in the PR, QRS, and QTc interval. This patient was considered to have ongoing silent ischemia and renal failure. Dr. Raman notes that several other patients might have underlying changes in hypocalcemia. However, during the first review cycle it was determined that OptiMark may interfere with the colorimetric analysis of calcium and cause an apparent lowering of the serum level. Whether the patients with hypocalcemia and ECG abnormalities had confirmed abnormal levels is not known. Therefore, definitive associations between underlying disorders could not be established.
Also, none of the patients developed severe or malignant arrhythmias.

Electrocardiographic Safety Assessment: Changes in ventricular repolarization may be associated with severe arrhythmias such as ventricular tachycardia. Prolongation of the QTc interval is considered to be a harbinger of ventricular arrhythmias. Clear predictive relationships have not been established on the amount of prolongation, the frequency of prolongation in an individual patient, and the frequency of prolongation in a population of patients. The OptiMark database provides evidence of some degree of QTc prolongation in essentially all patients who had frequent monitoring.

However, only a smaller fraction of these patients had prolongation of >30-60 mseconds (approximately 4%) and >60 mseconds (approximately 1-2%). Significant arrhythmias were not reported; however, the patients were not continuously monitored. Definitive associations with underlying disease or medications could not be made and the case report forms were not available in 7 patients who had QTc prolongation of > 30 mseconds.

Overall, these data raise the possibility that OptiMark is associated with QT interval prolongation. However, the pharmacologic and clinical relevance of these findings is not clear. There are several research reports in the literature about the ability of gadolinium to block the calcium channel. To resolve the dilemma, additional studies are needed. These would include animal studies to evaluate repolarization effects of OptiMark and its dose relationships. A sufficient number of animals and range of doses should be studied. Also, comprehensive continuous monitoring studies over a wide range of doses should be completed in patients.

C. Other Safety Comments

In addition to the electrophysiologic concerns discussed above, there are three other areas for clarification. These areas are 1) volume and local irritation relationships, and 2) a clarification the adverse event relationships in patients with a history of iodinated contrast allergic reactions and in patients with concomitant use of corticosteroids.

1) Volume and Local Irritation

One of the three submitted NDAs (#20,975) is for a pharmacy bulk package. The pack is proposed in a 50 mL vial. In the action letter of December 23, 1998, the sponsor was requested to provide a justification for the larger vial.

In response the sponsor indicated that it was for convenience in dosing and to accommodate the size of patients who enter the magnet. The sponsor proposed a dosing chart that lists the highest dose as 30 mL. Also, the sponsor proposed adding a statement that OptiMark is not indicated for magnetic resonance angiography or for delivery with power injectors.

Additionally, the sponsor submitted data that indicate that greater that 200 patients received volumes from approximately 35 to 118 mL. However, local adverse events in these patients were not analyzed. Also, in the adverse event table local events that might arise from the injection of larger volumes are listed in several body systems; e.g., body as a whole, cardiovascular and skin/appendages. The terms include local irritation, application site reaction and thrombophlebitis. ***In order to clarify the local adverse event profile, an analysis of local events by volume will be requested.***

2. Possible iodinated contrast allergy relationship and clarification of adverse events in patients who received Corticosteroids.

During the first review cycle, Dr. Raman noted that 40 to 60% of the patients in several studies (#484, 485,488, 538, & 543) had a previous history of iodinated contrast allergy, had an adverse event. A similar analysis of patients who did not have this allergic history is not available. ***This will be requested as part of the safety update.***

Also, Dr. Raman noted that 6 to 24% of the patients in various studies had concomitant treatment with corticosteroids at the time OptiMark was injected. ***An analysis of the adverse events by the presence or absence of corticosteroids will be requested.***

CONCLUSIONS:

The resubmission of the NDAs for OptiMark Injection in glass syringes, plastic syringes and a pharmacy bulk pack have been reviewed and found to be approvable with labeling revisions, clarifications on the adverse event profile and a phase 4 commitment.

ACTION: Approval if the following commitments and labeling issues can be resolved.
Otherwise Approvable

INDICATIONS:

1. OptiMARK® Injection is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues.

2. OptiMARK® Injection is indicated for use with MRI in patients who are highly suspect for liver abnormalities to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver.

LABELING:

PHASE 4 COMMITMENT:

1. Pre-clinical cardiac electrophysiologic studies: These should evaluate action potentials and various conduction channels (e.g., potassium and calcium) in an appropriate animal model. A wide range of doses should be studied to provide an adequate margin of safety based on body surface area conversion.

2. Expanded clinical cardiographic monitoring studies: These should be conducted in patients with a wide range of doses. Patients should be monitored continuously and all tracings should be retained and analyzed.

OTHER SAFETY COMMENTS:

1. Subgroup analysis of local adverse events by volume
2. Subgroup analysis of all adverse events by patients with and without a history of allergic iodinated contrast reactions.
3. Subgroup analysis of all adverse events and allergic events by patients with and without concomitant corticosteroids

_____

Patricia Y. Love, M.D.

EFFICACY ATTACHMENTS

Results of MRI Central Nervous System Studies with 0.1 mmol/kg OptiMARK® Injection		
Endpoints	Study A OptiMARK® ∇N = 132	Study B OptiMARK® N = 129
Conspicuity: Difference of Means (a)	0.39 *	0.66*
Worse	24 (18%)	24 (19%)
Same	69 (52%)	52 (40%)
Better	39 (30%)	53 (41%)
Border Delineation : Difference of Means	0.70 *	0.86 *
Worse	23 (17%)	25 (19%)
Same	55 (42%)	51 (40%)
Better	54 (41%)	53 (41%)
Number of Lesions: Difference of Means Pre Pair (b)	 1.8 2.0 ◆	 3.0 3.3*
Worse	9 (7%)	16 (12 %)
Same	101 (77%)	86 (67%)
Better	22 (16%)	27 (21%)
Confidence in Number of Lesions: Difference of Means	 0.11	 0.56 *
Worse	19 (14%)	18 (14%)
Same	86 (65%)	60 (47%)
Better	27 (20%)	51 (40%)

(a) Difference of means = (Side-by-side pre and post OptiMARK®) - (pre mean)
(b) Pair = Side-by-side pre and post Optimark

- **Statistically significant for both the median (Wilcoxon test) and mean (paired t test)**

◆ **Statistically significant for median (Wilcoxon test)**

∇ **1 patient was excluded from this analysis because a non-contrast image was not obtained for that patient**

Results of MRI Liver Studies with 0.1 mmol/kg OptiMARK® Injection		
Endpoints	Study C OptiMARK® N = 99	Study D OptiMARK® N= 100
Conspicuity: Difference of Means (a)	0.77 *	0.75*
Worse	21 (21%)	14 (14%)
Same	37 (37%)	50 (50%)
Better	41 (41%)	36 (36%)
Border Delineation: Difference of Means	0.77 *	0.69 *
Worse	21 (21%)	15 (15%)
Same	38 (38%)	45 (45%)
Better	40 (40%)	40 (40%)
Number of Lesions Pre Pair (b)	 2.4 3.0 *	 3.5 3.8 ▲
Worse	13 (13%)	16 (16%)
Same	50 (51%)	58 (58%)
Better	36 (36%)	26 (26%)
Confidence in Number of Lesions Seen: Difference in Means	1.6*	1.0*
Worse	**39 (39%)**	**38 (38%)**
Same	**2 (2%)**	**8 (8%)**
Better	**58 (59%)**	**54 (54%)**

(a) Difference of means = (Side-by-side pre and post OptiMARK® mean) - (pre mean)
(b) Pair = side-by-side pre and post OptiMARK®
*** Statistically significant for both the median (Wilcoxon test) and mean (paired t test)**
▲ Borderline statistical significance in paired t test

DIVISION DIRECTOR MEMO TO THE FILE

NDA:	20-937 (Parent NDA in Glass Vials) 20-975 (Plastic Syringes) 20-976 (Pharmacy Bulk Pack)
DRUG:	Optimark (Gadoversetamide) Injection
CLASS:	Gadolinium Contrast Agent
ROUTE:	Intravenous Injection
INDICATION:	Contrast Enhancement in CNS and Liver
MODALITY:	MRI (Magnetic Resonance Imaging)
CATEGORY:	1S - Original Submission
SPONSOR:	Mallinckrodt, Inc.
SUBMITTED:	March 02, 1998
PDUFA 10 Month:	January 02, 1998
12 Month	March 02, 1998
COMPLETED:	December 10, 1998

RELATED REVIEWS:

Chemistry - D. Place, Ph.D; 12/08/98
Clinical - R. Raman, M.D.; 12/04/98; E. Jones, 12/04/98
Microbiology - B Uratani, Ph.D.; 4/24/98
Pharmacokinetics - YM Choi, Ph.D; 11/03/98
Pharmacology - J Melograna, MS; 12/03/98
Statistics - R. Davi, Ph.D.; 11/06/98
Project Manager - J. Moore, RPh, MA.

RELATED DRUGS:

Currently 3 gadolinium based drugs are marketed in the US for contrast enhancement in MRI. These are Magnevist, ProHance, and OmniScan. These 3 drugs were first approved in 1988, 1992, and 1993 respectively. Their approved indications are similar and are summarized in table 1. The device technology is progressing towards additional indications. All are marketed in glass vials. Omniscan and ProHance also are in plastic syringes.

Table 1: Approved MRI Drugs and Their Indications

Drug	CNS (Brain)[a]	Spine & Associated Tissue	Body[b]	Head & Neck	Dose	
					0.1 mmol/kg	0.2 mmol/kg [c]
Magnevist	x	x	x	x	x [d]	
OmniScan	x	x	x		x	x [e]
ProHance	x			x	x	x

(a) Adults and pediatrics over 2 years
(b) Body is considered to be intrathoracic (excluding the heart) and intraabdominal regions
(c) As a second dose if needed for MRI of CNS
(d) Has upper limit of 20 mL
(e) Dosing chart highest total volume is 78 mL; also approved for bolus injection

BACKGROUND:

Optimark (gadoversetamide) Injection was developed by Mallinckrodt, Inc. as a contrast agent to enhance Magnetic Resonance Imaging. Magnetic Resonance Imaging (MRI) reflects proton alignment within a magnetic field by detecting differences in proton density, changes in longitudinal (T1) and transverse (T2) relaxation time. When drugs that interact with the magnetic field are introduced, they can affect the T1 and/or the T2 relaxation times and thus change the detect contrast (signal intensity) within an organ or tissue. Optimark is submitted to primarily affect T1 imaging and has been developed for the following proposed indications:

> *"Optimark injection is indicated for use with MRI in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood brain barrier. Optimark injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.*
>
> *"..... for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues"*
>
> *..... for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions in the liver"*

The first two indications for intracranial lesions, and spine and associated tissues are analogous to the language labeling of the CNS (brain), spine and associated tissues indications for the other approved gadolinium agents. The other gadolinium agents do not have a specific liver indication. The body indication labeling includes language such as intrathoracic (excluding) the heart and intraabdominal regions.

All discipline reviews are complete and contain either approval or non-approval recommendations. The microbiology, pharmacology-toxicology, and pharmacokinetic-pharmacodynamic portions of the application are acceptable for approval with labeling revisions. The clinical primary reviews recommended non-approval of efficacy and safety. However, on consideration of these issues, they are resolvable with labeling and phase 4 commitments. There are, however, significant chemistry deficiencies that render the application not-approvable at this time. This memorandum will concentrate on the deficiencies, policy, and labeling points.

CHEMISTRY

Optimark (gadoversetamide) for Injection is a non-ionic gadolinium chelated of diethylenetriamine pentaacetic acid bismethoxyethylamide. Its chemical name is [8,11-bis(carboximethyl)-14[2-[2-methoxethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)] gadolinium. The molecular formula is $C_{20}GdH_{34}N_5O_{10}$; the molecular weight is 661.77 g/mol. Optimark's structure is shown below.

STRUCTURE

Dr. Place's review notes that the application lacks any information on a critical component, calcium versetamide. The sponsor lists the components of Optimark as noted in the following table. Versetamide is the ligand that binds gadolinium and can bind to other anions. The sponsor notes that free versetamide is added to "stabilize" the gadoversetamide. However, as noted by Dr. Place, when calcium hydroxide and calcium dihydrate are added during manufacturing, the calcium exchanges with versetamide and forms calcium versetamide. This results in an agent with both gadoversetamide and calcium versetamide (as well as free gadolinium). The presence, formation, and stability of calversetamide is not sufficiently documented[1]. For details, please see Dr. Place's review.

Table 2: OPTIMARK COMPONENTS (*)	
Gadoversetamide	330.9 mg
Versetamide	mg
Calcium hydroxide	mg
Calcium dihydrate	
Sodium hydroxide	q.s.
Hydrochloric acid	pH adjust
Water for injection	q.s

(*) As proposed by Mallinckrodt

To resolve this deficiency, Dr. Place requests data on 1) the "manufacture and full characterization of calversetamide reference standard, 2) update the drug product specifications to reflect actual chemical composition., 3) revise the manufacturing instructions and associated documentation to incorporate controls that assay for calversetamide, and 4) establishment and validation of regulatory methods that determine calversetamide content and limits at time of manufacture and over the proposed expiry period".

EA - the environmental assessment is acceptable
EIR- Warning Letter Issued by Compliance.

During what was to be a pre-approval inspection, compliance noted a number of "significant

[1] These data were requested in a meeting with the sponsor in 1993 and in pre-NDA discussions.

systemic deficiencies" . The pre-approval inspection was stopped and deferred until the general deficiencies are resolved. Compliance recommended a "withhold approval". The systemic deficiencies noted in the GMPs of Mallinckrodt's approved products include the failure to reject lots as required by Mallinckrodt's SOPs. The report indicates that the released lots had particulate/glass matter, poor seals. These lots were not recalled, inspected nor were methods corrected. A Warning letter was issued to Mallinckrodt.

Dr. Place recommends non-approval and I agree with the recommendation. Calcium versetamide affects the toxicity profile of gadoversetamide[2], thus its amount and control are critical to the safety use of Optimark. The manufacturing site deficiencies are major and affect all products manufactured at that location.

MICROBIOLOGY

Optimark is a terminally sterilized product. The sterility assurance portion of the NDAs for the glass vial, plastic syringe and pharmacy bulk pack were reviewed by Dr. Brenda Uratani. The relevant portions of the submission were found to be acceptable and Dr. Uratani recommends approval. The details are in her review and I agree with the recommendation.

PHARMACOLOGY-TOXICOLOGY

Optimark is proposed for an injected dose of 0.1 mmol/kg (0.2 mL/kg) as a rapid intravenous bolus rate of 1.0 mL/min/kg. In support of this dose approximately 73 pre-clinical studies were conducted with various components of Optimark. These were reviewed by Dr. Melograna and Dr Laraine Meyers who recommend approval. I agree with this recommendation. For supportive details, please see Dr. Melograna's review. Several points will be summarized below.

Dr. Melograna's review frequently references tested formulations by number. MP-1177/10 is the proposed for market Optimark formulation containing the added calcium to form calcium versetamide. This was used in all key pharmacology and toxicology studies. The MP-1196 test product is versetamide without calcium. The toxicity of calcium versetamide alone was not studied. However, the MP-1177/10 final formulation contains the calcium versetamide as administered to humans.

The pharmacokinetics of Optimark in rat, dog and monkey animal models appears to be sufficiently similar to that of humans to allow for inferences on how Optimark will affect humans. Optimark is predominantly excreted by the kidneys with approximately 5% of radiolabeled gadolinium found in the feces. Also, radiolabeled Optimark is excreted in milk and crosses the placenta and was found in the rat fetus. (Melograna, pg 18-19). *This should be noted in labeling.*

Several cardiovascular and hemodynamic studies were done and are discussed in Dr. Melograna's review pg 28-32. Collectively they reveal effects on blood pressure, heart rate and LV systolic pressure at 30 - 60 sec after injection. These effects occur at or near the

---

[2] There are literature reports of gadolinium effects on calcium channels. Calcium ligands are added to other gadolinium MRI drugs to stabilize the gadolinium. The optimum amounts and stability are characterized in approved gadolinium MRI drugs.

recommended human dose based upon body surface area. Premature ventricular contractions were noted but a detailed electrophysiologic study was not conducted. Electrocardiographic interval changes are reported as normal, although the method of QTc correction was not provided. These studies were performed in anesthetized dogs, so the effects of anesthesia can not be eliminated.

CNS direct toxicity was evaluated by intracisternal injection in a rat model. Dr. Melograna notes (page 43-47, 104-107) that the dose estimates for brain exposure are apt to be excessive. Nevertheless, the data provide a worst case assessment. Adverse events of dyspnea, seizures, and tremors were noted at 21 x MHD estimated intracranial exposure.

Several multiple dose and special studies reveal target organ toxicity in the kidney, CNS (depressed motor function similar to that described in the preceding paragraph), and the male reproductive system (decreased sperm count and germ cells). Renal toxicity is similar to that of other gadolinium containing imaging drugs and is reflected in renal tubular vacuolization. In reproductive toxicity studies after multiple doses of Optimark 2.0 mmol/kg x 7 days, irreversible decrease in spermatogenesis and epidymides at the human dose adjusted for body surface area. In single dose studies, the NOEL is 0.5 mmol/kg (at the MHD adjusted for body surface area).

In developmental toxicology studies of a rat model after doses of Optimark 4.9 mmol/kg during days 7-17 of gestation, the fetuses had retarded growth , abnormal liver lobulation, delayed ossification, forelimb flexures, and cardiovascular changes of thoracic artery malformations, abnormal ventricles and septal defects. The NOEL is 0.7 mmol/kg (approximately the MHD adjusted for body surface area). These effects were found in two studies. Similar findings were found a lower levels in the historic controls. The reproductive and developmental toxicity results should be included in the labeling. The cardiovascular safety issues are discussed further in the clinical safety section below.

CLINICAL PHARMACOKINETICS & PHARMACODYNAMICS

The PK and PD portions of the NDA were thoroughly reviewed by Dr. Young Moon Choi and these are succinctly presented in his review. Based upon the submitted data, Dr. Choi recommends approval with labeling revisions. I agree with this recommendation. A few relevant conclusions that should be incorporated in the labeling are mentioned briefly in the next paragraph

As with other gadolinium MRI agents Optimark is primarily an intravascular drug that distributes rapidly into the ECF and has low protein binding (approximately 2%). The pharmacokinetics appear to be linear within the proposed dose range. Dr. Choi's review (pg 7-8) notes that the two compartment model underestimates the terminal half life. Recalculated data using a non-compartment model are attached to his review page 11 and 12. These results are used in the labeling. Based upon Dr. Choi's analysis, the elimination $t_{½}$ is 1.73 hours. Optimark is not metabolized and 95 % of the injected dose is eliminated intact in the urine by 72 hours. Clearance is based on the glomerular filtration rate. In renally impaired patients, the elimination t ½ is 4x higher than in normal men (8.74 vs 1.73 hr) and 4x than in normal women (6.91 vs 1.73 hr). These comparisons are tabulated in Dr. Choi's review page 13 and are derived from several studies as footnoted in his table. In comparison to normal subjects, there are slightly increase in the elimination t ½ in patients with CNS disease (1.90 in men and 1.94 in women) and hepatic impairment (2.09 in men; 2.35 in women). These differences do not appear to be clinically

significant. Optimark was evaluated in 8 renal failure patients on hemodialysis. Based upon 3 dialysis sessions over 5 days, 98% of Optimark was cleared.. The mean dialysis clearance was approximately half of the creatinine clearance (see Choi pg 39). Optimark, as other gadolinium drugs, the gadolinium can affect zinc levels by ion exchange.

CLINICAL & STATISTICAL

As noted in the introductory background, the Optimark application requests approval for MRI imaging in the brain and spine, and in the liver. The clinical and statistical portions of the NDA were reviewed by Drs. Davi, Raman, and Yaes. Dr. Yaes reviewed the key studies in support of the liver indication, Dr. Raman reviewed the key studies in support of the brain and spine indications, the phase 1, and 2 supportive data, and the safety data. Dr. Davi reviewed the statistical portions of the liver, and the brain and spine indications. Dr. Davi's review indicates that the statistical portion of the key studies is acceptable with caveats on the type of statistical analysis that is performed. The sponsor will be asked to verify an alternative analysis. The medical reviews recommend non-approval for safety and efficacy. Dr. Jones, medical team leader, recommends approval with labeling and phase 4 commitments. After consideration of these issues, I agree that sufficient information is provided for approval with labeling restrictions. These issues will be addressed in this section. Overall the clinical development plan, the demographics of patients in all phases of development, and the regulatory history of Optimark are well summarized in Dr. Raman's review pg 1- 11 and are amplified in his study description sections. These points will not be amplified in this memorandum.

The key clinical trials for the brain and spine (subsequently referred to as central nervous system-CNS) and the liver indications used a similar trial design. Consequently the design issues are the same and will be discussed collectively. The major issues raised by the reviewers are the standard of truth, clinical relevance of end points, method of image interpretation, and the analytical method.

Both the CNS and liver studies used enriched populations. The CNS trial enrolled subjects with a suspicion of CNS pathology and with a "qualifying" MRI . It appears that the qualifying MRI could be with or without contrast from any approved gadolinium drug. In the liver study, the patients had a qualifying CT. Based upon the reviewers inquiries to the sponsor, apparently this qualifying MRI or CT identified patients with pathology. Also, the qualifying MRI or CT was used as part of the final diagnosis. For both trials, after enrollment the patients had a second non-contrast and contrast MRI. The second non-contrast MRI could be used as part of the final diagnosis. The study contrast MRI was not part of the final diagnosis. Given this design, in both trials Optimark is tested for its ability to add additional information after an abnormal MRI or CT in patients who are highly suspect for disease. The analysis is conducted in comparison to the non-contrast MRI and to the final diagnosis. An analysis in comparison to the qualifying MRI or CT was not submitted. A systematic approach to confirm the MRI findings was not part of the study design. How the information would be used in subsequent diagnostic or therapeutic management was not evaluated for the appropriateness of the decisions.

Both the CNS and liver studies had 2 identical primary endpoints: the conspicuity of the lesions and the delineation of the lesions. Also, the CNS and liver studies had a 3rd primary endpoint about the confidence in the interpretation. In the CNS studies, the endpoint was worded as degree of confidence in the number of lesions. In the liver studies it was worded as the degree of confidence in the diagnosis. All three endpoints were scored on a 1-10 analogue scale (where 1=

no confidence/no visualization/no lesions, and 10 = extreme confidence/clearly visualized). Supportive secondary endpoints included the number of lesions and the agreement with the final diagnosis. The latter was scored as either not evaluable (not technically adequate to determine); no agreement; partial (incomplete); basic (agree in diagnosis, but not in number or location of lesions); complete (agree in diagnosis, number of lesions, location of lesions) to complete agreement. For the statistical analysis basic and complete agreement were scored as agreement, the others as not in agreement.

The reviewers appropriately note that in this enriched population, the final diagnosis is not apt to change. Differences are more apt to be in the number of lesions, conspicuousness of the lesion and its border delineation. The clinical impact (effect on management) of these technical features was not studied.

Images were read by 3 blinded readers, each of which read 1/3 of the data set. [This is comparable to a 3 site single reader assessments, but it does not allow for inter-reader assessments.] The images were presented in a format that is a variant of the typical pre and post readings used in imaging studies. In these studies the images were presented in sets of 4. The first 3 images always were pre images and consisted of the T1, T2 and proton density films. The 4th image was either a repeat of the T1 pre image, or it was the T1 with contrast. Contrast images were never viewed alone. This format was found to be acceptable in part because of the systematic approach and the preservation of blinding. *However, labeling should note that Optimark is not approved as a "stand-alone" without contrast.*

The primary objective of the study was to demonstrate Optimark's equivalence to Magnevist. Equivalence is based upon a mathematical formula that relates the differences of the mean. Equivalence is defined as a calculated value of 1.5 to - 1.5. According to Dr. Davi's simulations, the greatest difference in analogue scores that could occur, and still meet the formula criteria, is 1.22 on the analogue scale. Data were not submitted to document the clinical relevance of this formula and the proposed equivalence range. Although not clear in the analytical plan, in order to establish equivalence the results would need to establish that a difference could be detected if it existed. Often this is done with an analysis to a placebo or other dose group. In this study a comparison to baseline could serve as a "placebo" for efficacy. Dr. Davi completed additional analyses in comparison to baseline and reported the number of patients who, in comparison to baseline, were better, worse or the same.

The reviewing medical officer of the liver studies (Dr. Yaes) raised additional concerns about the ability to approve the liver indication without a more systematic standard of truth. Technically Magnevist is not approved for liver MRI. It does have, however, an indication for body (intrathoracic (excluding the heart) and intra-abdominal) areas. This includes the liver.

Also, a non-cross over design will be general performance information for the population. However, to test actual imaging performance for potential differences in the number of lesions, delineation and other information used in a diagnosis, a cross over study of Magnevist and Optimark would be needed.

The points raised thus far in this section will be discussed further in the summary section for each indication.

Results:

1. CNS

Overall 403 patients were enrolled in two key studies for the CNS indication. Of these, 394 were evaluable (i.e, 200 in study #488; 194 patients in study # 525). Please see Dr. Raman's review page 6-10 for additional demographic and study details. Of the evaluable patients, 69% had images of the brain, 31% images of the spine. the representative disorders at final diagnosis were approximately tumor (32%), demyleinating or degenerative (30%), vascular 12%, normal 8%, other (8%), unknown 7%, infection or inflammation 5%, and trauma 3%. Also, of these patients approximately 41% had previous treatment (chemotherapy, radiotherapy or surgery). As noted in Dr. Ramesh's review page 108, such treatments are felt to permanently alter the blood brain barrier.

The following table describes the primary and supportive secondary endpoints of both studies. The first column Lists the primary endpoints of the confidence in the number of lesions, the conspicuity of the lesions, the border delineation. These rows report the difference in the mean (i.e, the mean analogue scale on the paired Optimark read minus the before Optimark mean). The other main category is the secondary endpoint of the number of lesions. This row lists the actual mean number of lesions before Optimark, and the paired Optimark image interpretation. The subheadings of each of these endpoints lists the number of patients for whom the Optimark images were worse, the same or better than the unenhanced images. As is evidence by the table, in patients who received Optimark, all but one primary endpoint reached statistical significance in the paired t test (per-protocol analysis). All primary endpoints reached statistical significance in the Wilcoxon test (Dr. Davi's analysis). For the number of lesions identified in all patients, a statistical significance was not noted. For the number of patients who were better, the same or worse after Optimark, on average for each primary endpoint, 38 - 50% of the patients were better, 31 -50% were the same, and 7 -19% were worse. For the number of lesions, 69 - 77% of the patient images were the same on pre and post Optimark images. Overall, these results are similar to those of Magnevist.

(Continued on the next page)

Table 3; BRAIN & SPINE
Comparison of Optimark and Magnevist Imaging Results of Key Endpoints

Endpoints	Study 488		Study 525	
	Magnevist N= 68	Optimark N = 132	Magnevist N = 65	Optimark N = 129
Confidence - Number of Lesions Difference of Means(a)	0.32	0.40 *	0.92 *	0.70 *
Worse	18 (26%)	28 (21%)	8 (12%)	25 (19%)
Same	26 (38%)	51 (39%)	20 (31%)	40 (31%)
Better	24 (35%)	24 (40%)	37 (57%)	64 (50%)
Conspicuity Difference of Means	1.05 *	0.39 *	0.89 *	0.66*
Worse	24 (18%)	5 (7%)	24 (19%)	9 (14%)
Same	69 (52%)	37 (54%)	52 (40%)	27 (42%)
Better	39 (30%)	26 (38%)	53 (41%)	29 (47%)
Border Delineation Difference of Means	0.91 *	0.70 *	1.2 *	0.86 *
Worse	23 (17%)	11 (16%)	25 (19%)	7 (11%)
Same	56 (42%)	28 (41%)	51 (40%)	29 (42%)
Better	54 (41%)	29 (43%)	53 (41%)	29 (45%)
Number of Lesions Pre Pair (_)	1.6 1.5	1.9 2.1 ◆	2.1 2.1	3.1 3.4
Worse	6 (9%)	9 (7%)	7 (11%)	14 (12 %)
Same	56 (82%)	103 (77%)	46 (72%)	83 (69%)
Better	6 (9%)	22 (16%)	11 (17%)	24 (20%)

(a) Derived from R. Davi's tables review page 24 - 33
(b) Difference = of means; (paired pre and post Optimark mean) - (pre mean)
© Pair = paired pre and post Optimark
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
◆ Statistically significant for median (Wilcoxon test) only

A subset analysis was performed by Dr. Raman & Davi of patients with previous treatment (chemotherapy, radiotherapy, or surgery) who are expected to have a persisting abnormality in the blood brain barrier (see Raman page 108 - 115). As shown in table 4 for study 488, in this subset there was a greater number of patients who had improved conspicuity, delineation and confidence than in those patients who did not have treatment. Dr. Davi's review page 16, reflects a similar assessment of these patients had demonstrates that the previously treated

patients have the greatest statistical significance over baseline, however statistically significant results are seen in the non-treated patients. (See a copy of this table attached to page 16 of this memorandum).

Table 4: Subset Comparison of the Number of Patients with and without Previous Treatment that had Improved Images After Optimark or Magnevist				
EndPoints	OptiMark (N=132)		Magnevist	
	Previous Treatment N = 55	No Treatment n = 77	Previous Treatment N = 28	No Treatment n = 40
Conspicuity	20 (36%)	19 (25%)	18 (64%)	9 (23%)
Confidence	28 (51%)	25 (32%)	13 (46%)	11 (28%)
Border	33 (60%)	21 (27%)	13 (46%)	15 (38%)

CNS summary: Suggests that the Optimark results are similar to Magnevist in providing contrast enhancemetn that increases conspicuity and border delineation. Also, in a subset of patients with known blood brain barrier abnormalities because of treatment, Optimark appears to demonstrate enhancement in a larger percent of patients. The extent to which this assists or hampers the image interpretations was not studied systematically with a definitive standard of truth (e.g. histopathology). As with other gadolinium agents, some images are more diagnostic without contrast, some are better with and some are the same. This is noted in the precautions section of other approved gadolinium containing MRI drugs. Without an inpatient assessment, Optimark can not be evaluated as equivalent to Magnevist. Therefore, overall I agree with Dr. Jones' recommendation that sufficient information has been submitted to demonstrate efficacy in the brain and spine. The labeling should reflect the enriched population, the limitations of the database, the need to interpret the paired images, and the fact that in some patients the pre-images are better than those with Optimark.

2. Liver Studies

Overall 410 patients were enrolled in two key studies for the liver indication. Of these, 396 were evaluable (i.e, 193 in study #490; 203 patients in study # 526). Please see Dr. Yaes' review page 26 & 47 for additional demographic and study details. Of the 199 evaluable Optimark patients in both studies. the representative disorders at final diagnosis were approximately tumor (92%), other/unknown 4%, vascular 3%, and infection/inflammation/trauma 1 %. Dr. Yaes review points out that only 4 patients were diagnosed and normal. Thererfore, these studies were conduced in a highly enriched population.

The summary statistics for the primary endpoints and supportive secondary endpoitns are shown in the following table. The table is forkmatted in the same manner as the CNS descritpive table above (see page 8 for table format).

As is evidence by the table, in patients who received Optimark, all but one primary endpoint reached statistical significance in the paried t test (per-protocol analysis). All primary endpoints

reached statistical significance in the Wilcon test (Dr. Davi's analysis). For the number of lesions identified in all patients, a statistical significance was noted. For the number of patients who were better, the same or worse after Optimark, on average for each primary endpoint, 36 - 69% of the patients were better, 14 - 50% were the same, and 15 - 21% were worse. For the number of lesions, 51-57% of the patient images were the same on pre and post Optimark images. Overall, these results are similar to those of Magnevist.

Table 5: LIVER STUDIES
Comparison of Optimark and Magnevist Imaging Results of Key Endpoints

Endpoints	Study 490		Study 526	
	Magnevist N = 94	Optimark N = 99	Magnevist N = 103	Optimark N= 100
Confidence- Diagnosis Difference of Means	1.41 *	1.46 *	1.01 *	1.2 *
Worse	12 (13%)	16 (16%)	18 (17%)	17 (17%)
Same	19 (20%)	14 (14%)	25 (24%)	19 (19%)
Better	63 (67%)	69 (69%)	60 (58%)	64 (64%)
Conspicuity Difference of Means	0.31	0.76 *	0.78 *	0.75*
Worse	22 (23%)	21 (21%)	13 (13%)	14 (14%)
Same	41 (43%)	37 (37%)	51 (50%)	50 (50%)
Better	31 (33%)	41 (41%)	39 (37%)	36 (36%)
Border Delineation Difference of Means	0.28 *	0.77 *	0.85 *	0.69 *
Worse	20 (21%)	21 (21%	14 (14%)	15 (15%)
Same	43 (46%)	38 (38%)	50 (49%)	45 (45%)
Better	31 (33%	40 (40%)	39 (38%)	40 (40%)
Number of Lesions				
Pre	2.5	2.4	3.1	3.4
Pair	3.0	3.1 ▲	3.6	3.8 *
Worse	18 (19%)	13 (13%)	15 (15%)	16 (16%)
Same	46 (49%)	50 (51%)	65 (63%)	57 (57%)
Better	29 (31%)	35 (35%)	23 (22%)	26 (26%)

(a) Derived from R. Davi's tables review page 24 - 33
(b) Difference = of means; (paired pre and post Optimark mean) - (pre mean)
(c) Pair = paired pre and post Optimark
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
▲ Borderline statistical significance in paired t test only

Liver summary: The above data suggests that the Optimark ability to detect lesions with vascular abnormalities is similar to that described in for the brain and spine. Also, as with other gadolinium agents, some images are more diagnostic without contrast, some are better with and some are the same. The results appear to be in the same direction as Magnevist, however, as with the brain and spine indication, without an inpatient assessment, Optimark can not be considered as equivalent to Magnevist.

The liver indication raises several policy issues some of which are discussed in Dr. Yaes review and include concerns about the lack of approval of Magnevist for MRI of the liver. Dr. jones' comments note that while equivalence to Magnevist is the objective of the study, it is not required for approval. Optimark has demonstrated improvement over baseline MRI.

Dr. Yaes also raises the question of the lack of a rigorous standard of truth to confirm the diagnosis. In considering this it is clear that the clinical setting was not well defined and a clear hypothesis to test how the information would be used was not established. On the other hand, these studies were conducted in a manner that is consistent with those of the other approved gadolinium agents. Also, the studies are done to define or locate anatomic structures, normal variants or pathology that can easily distingquished from normal anatomy. They are not performed to make definitive diagnoses such as the distinction of benign and malignant disease. This is further supported by the fact that the final diagnosis before and after OptiMark and Magnevist is very similar to pre diagnosis. Therefore, considering the liver indication as an anatomic or structural one, then a rigorous standard of truth is not needed[3].

A larger issue is whether to approve a liver only indication when the other MRI agents are approved for other areas of the abdomen and intrathoracic area. At present the division does not have a policy on whether the benefit demonstrated in intrabomenal organ can be extrapolated to other similar organs. (Conversely data from a number of organs or structures within the abdomen and intrathorax (except the heart) is considered sufficient for a non-organ specific indication; e.g., "body" as listed in the introductory background section of this memorandum.) Therefore, until a policy is established, the indication should be limited to the liver with appropriate labeling restricitions.

SAFETY

Overall 1663 patients exposed to Optimark, 515(31%) reported at least 1 adverse event (AE). This compares to 34.7% of Magnevist patients who reported at least 1 AE. Of these there were 8 deaths and 8 serious events. The deaths did not occur during the study period and appear to be related to the underlying disease. These are discussed in Dr. Raman's review page 173 and summarized in an appendix on page 219. Of the serious events in 8 patients, the sponsor attributed all to underlying disease. In Dr. Raman's summary (page 174), he notes that 4 are probably due to underlying disease. The other 4 events are difficult to interpret and include, two patients with seizure and post-ictal phenomena, one patient with nausea and vomiting, and a renal dialysis patient with dizziness, palpitations, dyspnea. Also, there were 4 patients who discontinued because of an adverse event. These included three patients with allergic "rash or

[3] If Optimark's mechanism of action was different from that of Magnevist (e.g., it had a ligand that was metabolized in order to reach the target organ), then additional studies and confirmation might be needed.

hives" due to Optimark, and one patient with seizures (either due to Optimark or subtherapeutic medication levels). The most common body system with adverse events is the body as a whole (217 (13%). Overall the most common adverse events are Headache 7.5%, taste perversion 5.7%, dizziness 3%, and nausea 2.6%. The details, the vital signs and laboratory are well summarized in Dr. Raman's safety review. His summary table of AEs is attached to this memorandum on pg 17-18.

The major safety issue raised in Dr. Raman's review relates to the assessment of the electrocardiographic (ECG) data. These are not systematically presented in a manner that can correlate ECG intervals and arrhythmias. Therefore, it is not possible to assess the potential for early electrophysiologic changes, and the possibility of transient but potentially life threatening arrhythmias. Specifcially, ECG data are not presented by the time points of collection. In approximately 160 patients, non-continuous ECG data were collected during the immediate injection period, 15, 30 and 60 minutes. Their data are summarized as a group. Most other patients had data after 2 hours. In the phase 3 studies, ECGs were collected at 24 hours. The lack of a systematic analysis obscures the ability to assess the risk. Additionally, the sponsor's ECG analysis for clinically significant deviations used upper and lower limites that are greater than those customarily used in clinical practice (see Raman page 185). This are listed in table 6.

Table 6: ECG Intervals Used to Determine Clinical Significance *

Interval	Sponsor (msec)	Typcial (msec)
PR	< 60; > 240	<120 ; > 240
QRS	< 40; > 160	< 50 ; >110
QT	< 200; > 500	< 360 ; >390 at 75 beats per minute

* Derived from Dr. Raman's pages 185-186

Based upon these intervals, Dr. Raman (pg 188 - 192) notes that ECG data in 421 patients reveal that in 56 (13 %) there is an increase in heart rate and a decrease in PR and QT interval, or some type of arrhythmia. Whether or how QT correction was made is not clear. There are at least 2 patients with reported QT prolongation in that was not further clarified. Also, in a phase 1 study of 20 patients, 11 had bradycardia at "some point during the study". One patient had bradycardia and AV dissociation with a HR of 39. The sponsor reported that this was secondary to a vasovagal reaction in an atheletic individual. Data to support this conclusion were not submitted. (See Raman page 31 for details). The pharmacology-toxicology data on electrocardiac toxicity is not conclusive.

Based upon these data, the potential for QT prolongation and life threatening arrhythmias has not been sufficiently evaluated. Additional cardiovascular safety study that include a correlation with calcium levels, and reanalysis of the existing ECGs are needed. Also, the labeling should warn of the lack of data during infusion and the immediate period when the Optimark blood levels are at their highest.

DSI - The inspection did not reveal any data that would affect the approval recommendation.

ASSESSMENT

The Optimark application contains sufficient data to approve its use in MRI imaging of the liver, brain, and the spine and associated tissues. However, the application is not approved because of significant chemistry, manufacturing controls, and overall plant deficiencies. Also, additional analysis of the electrocardiographic data are needed. The extent to which additional clinical or mechanistic studies can not be determined until the requested ECG analysis and chemistry data are submitted and reviewed.

ADDITIONAL COMMENTS - NDA 20-975 (Plastic Syringes); NDA 20-976 (Pharamcy bulk Pack)

All of the preceding portions of this memorandum affect all three NDAs. The following comments affect only the plastic syringe and pharmacy bulk pack. These two NDAs contained chemistry and pharmacology data on excipients. Pharmacology recommended these applications as approvable pending resolution of issues from other disciplines. However, there are a few additional chemistry issues for each application.

For the plastic syringes, the application lacks consistency in the regulatory specification for the drug substance and the drug product, the SOP on inspection and testing of rubber stoppers (2-12) lacks data on the controlling of the siliconization process and the extent to which silicon oil leaches into the drug product; and he SOPs lack sufficient information to ensure the prevention of sampling lapses in the stability procedures. These issues are included in the action letter.

For the pharmcy bulk pack, the application lacks a full description of the actual extractibles from the elastomeric syringe piston. Additionally, the pharmacy bulk pack contains 50 ml in a non-preserved container. This means the seal can be punctured only once and, apparently will be used for only one patient. Optimark is submitted with proposeed dosing recommendations of 0.1 mmol/kg. The Optimark concentration is 0.5 mmol/ml. For the proposed dose in phase 3 studies, the average volume administred was 15 ml with an upper range of approximately 35 ml. The calculated volumes needed to administer the 0.1 mmol/kg dose in patients of different weights are shown in the next table.

Table 6: Optimark Dose by Volume

Dose	Weight (kg)	Volume (ml)
0.1 mmol/kg	70 kg	14 ml
	150 kg	30 ml
	250 kg	50ml
0.3 mmol/kg	70 kg	42 ml
	83 kg	50

This table shows that for the requested dose, a patient would need to weight 250 kg. Most MRI scanners can not accommodate patients of such size. It should be noted that in phase 1 & 2 the sponsor explored higher doses up to 0.5 mmol/kg (in approximately 250 patients) and 0.7 mmol/kg in 4 patients. The adverse event profile suggest an increase in reported frequency and severity of adverse events with increasing dose (see AE tables on page 17-18).

The NDAs for the glass and plastic syringes meet the needs of the proposed doses and volumes. The larger volume of the pharmacy bulk pack is apt to be used in off labeled indications of either higher concentrations (0.3 mmol/kg approved in two gadolinium agents for CNS imaging) or for use in magnetic resonance angiography. The latter uses volumes of 40 to 60 ml. At this point the sponsor has not provided information to justify the approval of the pharmacy bulk pack.

ACTION for all 3 NDAs - Not Approvable

LETTER

A. Non-approval issues for chemistry and inspection

These should be listed by the overall NDA, and separate NDAs where appropriate

B. Other issues

!. Clinical

a. Reread of available ECGs to fully discribe and analysis the intervals and arrhythmias
b. Advise of the possibile need of additional cardiovascular safety study to determine the events during and immediately after injection. This should include calcium levels as well.
c Request confirmation of Dr. Davi's statistical analysis
d. Request a justification for the pharmacy bulk pack

2. Clinical Pharmacokinetics & Pharmacodynamics

Request verification of Dr. Choi's PK analysis

3. Labeling deferred until otherwise approvable

INTERNAL COMMENTS

1. Labeling should include

Imaging with T1, T2, and proton density as the non-enhanced image comparator
Precautions on male reproductive and fetal risks

Table 8: Study 488 – Mean Change in Primary Endpoints by Post-treatment Patient Grouping

Endpoint	Patient Status	Treatment Group	Mean Difference (pair-pre)	Standard Deviation of Differences	t-test p-value
Conspicuity	Post-Treatment	Optimark n=55	0.5273	2.1418	0.0734
		Magnevist n=28	1.7857	1.9693	0.0001
	Non-Post-Treatment	Optimark n=77	0.2987	2.1464	0.2258
		Magnevist n=40	0.5500	2.4802	0.1687
Border Delineation	Post-Treatment	Optimark n=55	1.1636	2.2752	0.0004
		Magnevist n=28	1.0714	2.3401	0.0224
	Non-Post-Treatment	Optimark n=77	0.3766	2.2422	0.1446
		Magnevist n=40	0.8000	2.3772	0.0397
Diagnostic Confidence	Post-Treatment	Optimark n=55	0.6545	2.1707	0.0295
		Magnevist n=28	0.8571	1.8402	0.0204
	Non-Post-Treatment	Optimark n=77	0.2208	1.6593	0.2466
		Magnevist n=40	-0.0500	1.3950	0.8219

Table 9: Study 525 – Mean Change in Primary Endpoints by Post-treatment Patient Grouping

Endpoint	Patient Status	Treatment Group	Mean Difference (pair-pre)	Standard Deviation of Differences	t-test p-value
Conspicuity	Post-Treatment	Optimark n=33	0.9091	2.8103	0.0723
		Magnevist n=16	1.6250	2.5528	0.0224
	Non-Post-Treatment	Optimark n=33	0.5729	3.3865	0.1007
		Magnevist n=16	0.6531	3.5092	0.1989
Border Delineation	Post-Treatment	Optimark n=33	1.1818	3.4951	0.0609
		Magnevist n=16	2.1875	0.7372	0.0096
	Non-Post-Treatment	Optimark n=33	0.7604	3.4205	0.0319
		Magnevist n=16	1.0000	3.8568	0.0758
Diagnostic Confidence	Post-Treatment	Optimark n=33	0.9394	2.8167	0.0644
		Magnevist n=16	1.3750	0.5836	0.0325
	Non-Post-Treatment	Optimark n=33	0.6250	2.4804	0.0153
		Magnevist n=16	0.7755	1.7472	0.0032

Derived from R. Davi's review

SAFETY: ADVERSE EVENTS*: OptiMARK™ : NDA # 20937
Subjects/Patients with an Adverse Event by Body System & COSTART TERM - N (%)

		Treatment Group								
		OptiMARK™ (mmol/kg)							Magnevist® (mmol/kg)	Placebo
		0.1	0.2	0.3	0.4	0.5	0.7	All	0.1	
Body System	Term	N=959	N=201	N=221	N=22	N=256	N=4	N=1663	N=329	N=46
Event	None	678 [70.7]	159 [79]	144 [65]	16 [73]	155 [61]	1-25	1153 [70]	215 [65]	24 [52]
	Any event	281 [30]	42 [21]	77 [35]	6 [27]	101 [40]	3-75	510 [31]	114 [35]	22 [48]
Number of patients with one or more AEs	One event	147 [16]	25 [12]	47 [21]	4 [18]	58 [23]	1-25		62 [19]	6 [13]
	Two events	66 [7]	8 [4]	10 [5]	2 [9]	21 [8]	1-25		30 [9.1]	4 [8.7]
	> two events	68 [7.1]	9 [4.5]	20 [9]	0	22 [8.6]	1-25		22 [6.7]	12 [26.1]
Body as a whole	Any event	141[(14.7]	11 (5.5)	32 (14.5)	2 (9.1)	31 (12.1)	0	217 (13.1)	63 (19.1)	12 (26.1)
	Headache	81 (8.4)	5 (2.5)	19 (8.6)	1 (4.5)	18 (7.0)	0	124 (7.5)	31 (9.4)	8 (17.4)
	Pain Abdomen	17 (1.8)	3 (1.5)	0	0	4 (1.6)	0	24 (1.4)	4 (1.2)	2 (4.3)
	Asthenia	13 (1.4)	1 (0.5)	2 (0.9)	0	4 (1.6)	0	20 (1.2)	8 (2.4)	2 (4.3)
	Inj. site reaction	16 (1.7)	0	3 (1.4)	0	1 (0.4)	0	20 (1.2)	10 (3.0)	2 (4.3)
	Pain - Back	9 (0.9)	0	5 (2.3)	0	2 (0.8)	0	16 (1.0)	3 (0.9)	0
	Pain	8 (0.8)	1 (0.5)	2 (0.9)	1 (4.5)	1 (0.4)	0	13 (0.8)	12 (3.6)	1 (2.2)
	Pain - Chest	7 (0.7)	0	2 (0.9)	0	2 (0.8)	0	11 (0.7)	1 (0.3)	0
	Chills	5 (0.5)	0	0	0	3 [1.2]	0	8 [0.5]	3 [0.9]	2 [4.3]
	Fever	4 [0.4]	2 [1.0]	0	0	2 [0.8]	0	8 [0.5]	2 [0.6]	0
	Inflam. Inj. Site	2 [0.2]	0	0	0	0	0	2 [0.1]	0	0
	Muc. Mem. Dis.	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Abnormal labs	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Pain – Substernal	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
	Lab test abnorm	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Flu syndrome	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Edema inj. Site	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Edema face	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Allergic reaction	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
Cardiovascular	Any event	38 [4.0]	17 [8.5]	21 [9.5]	3[13.6]	27 [10.5]	3-75	109 [6.6]	10 [3.3]	4 [8.7]
	Palpitation	6 [0.6]	0	0	0	1 [0.4]	0	7 [0.4]	1 [0.3]	0
	Hypertension	3 [0.3]	0	1 [0.5]	0	0	0	4 [0.2]	0	1 [2.2]
	Postural hypotension	3 [0.3]	0	0	0	0	0	3 [0.2][@]	0	0
	Pallor	1 [0.1]	0	1 [0.5]	0	0	0	2 [0.1]	0	0
	Tachycardia	2 [0.2]	0	0	0	0	0	2 [0.1][@]	1 [0.3]	0
	Hypotension	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Syncope	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Arrhythmia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
Digestive	Any event	58 [6.0]	10 [5.0]	15 [6.8]	0	23 [9.0]	0	106 [6.4]	20 [6.1]	7 [15.2]
	Nausea	29 [3.0]	2 [1.0]	6 [2.7]	0	6 [2.3]	0	43 [2.6]	8 [2.4]	4 [8.7]
	Diarrhea	12 [1.3]	5 [2.5]	3 [1.4]	0	9 [3.5]	0	29 [1.7]	3 [0.9]	1 [2.2]
	Dyspepsia	7 [0.7]	2 [1.0]	3 [1.4]	0	4 [1.6]	0	16 [1.0]	2 [0.6]	3 [6.5]
	Vomit	7 [0.7]	2 [1.0]	1 [0.5]	0	2 [0.8]	0	12 [0.7]	3 [0.9]	1 [2.2]
Hemic & Lymphatic	Any event	5 [0.5]	1 [0.5]	4 [1.8]	0	3 [1.2]	0	13 [0.8]	5 [1.5]	0
	Ecchymosis	5 [0.5]	0	4 [1.8]	0	2 [0.8]	0	11 [0.7]	5 [1.5]	0
	Thromb.penia	0	1 [0.5]	0	0	0	0	1 [0.1]	0	0
Metabolic & Nutritional	Any event	6 [0.6]	1 [0.5]	4 [1.8]	0	4 [1.6]	0	15 [0.9]	0	0
	Edema	2 [0.2]	0	2 [0.9]	0	2 [0.8]	0	6 [0.4]	0	0
	Edema – periph.	1 [0.1]	0	2 [0.9]	0	1 [0.4]	0	4 [0.2]	0	0
	Hypercalcemia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Hyperglycemia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Hypoglycemia	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
	Hyponatremia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Creatinine	0	1 [0.5]	0	0	0	0	1 [0.1]	0	0
Musculoskeletal	Any event	14 [1.5]	1 [0.5]	0	0	4 [1.6]	0	9 [1.1]	3 [0.9]	2 [4.3]
	Myalgia	5 [0.5]	1 [0.5]	0	0	1 [0.4]	0	7 [0.4]	1 [0.3]	1 [2.2]
	Arthralgia	3 [0.3]	0	0	0	2 [0.8]	0	5 [0.3]	1 [0.3]	0
	Cramps – leg	4 [0.4]	0	0	0	0	0	4 [0.2]	1 [0.3]	0

SAFETY: ADVERSE EVENTS*: OptiMARK™ : NDA # 20937
Subjects/Patients with an Adverse Event by Body System & COSTART TERM - N (%)

		Treatment Group								
		OptiMARK™ (mmol/kg)							Magnevist® (mmol/kg)	Placebo
		0.1	0.2	0.3	0.4	0.5	0.7	All	0.1	
Body System	Term	N=959	N=201	N=221	N=22	N=256	N=4	N=1663	N=329	N=46
Event#	None	678 [70.7]	159 [79]	144 [65]	16 [73]	155 [61]	1-25	1153 [70]	215 [65]	24 [52]
	Any event	281 [30]	42 [21]	77 [35]	6 [27]	101 [40]	3-75	510 [31]	114 [35]	22 [48]
Number of patients with one or more AEs	One event	147 [16]	25 [12]	47 [21]	4 [18]	58 [23]	1-25		62 [19]	6 [13]
	Two events	66 [7]	8 [4]	10 [5]	2 [9]	21 [8]	1-25		30 [9.1]	4 [8.7]
	> two events	68 [7.1]	9 [4.5]	20 [9]	0	22 [8.6]	1-25		22 [6.7]	12 [26.1]
Nervous	Any event	66 [6.9]	4 [2.0]	18 [8.1]	2 [9.1]	22 [8.6]	2-50	114 [6.9]	20 [6.1]	11 [23.9]
	Dizziness	30 [3.1]	1 [0.5]	9 [4.1]	0	10 [3.9]	0	50 [3.0]	7 [2.1]	7 [15.2]
	Paresthesia	20 [2.1]	1 [0.5]	2 [0.9]	0	6 [2.3]	1-25	30 [1.8]	7 [2.1]	2 [4.3]
	Convulsion	3 [0.3]	0	2 [0.9]	0	1 [0.4]	0	6 [0.4]	0	0
	Hypesthesia	2 [0.2]	1 [0.5]	1 [0.5]	0	0	0	4 [0.2]	0	0
	Hypertonia	2 [0.2]	0	1 [0.5]	0	0	0	3 [0.2]	1 [0.3]	0
	Depersonal.	0	0	1 [0.5]	0	0	0	1 [0.1]	0	0
	Confusion	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Tremor	1 [0.1]	0	1 [0.5]	0	0	0	2 [0.1]	0	1 [2.2]
Respiratory	Any event	29 [3.0]	2 [1.0]	7 [3.2]	0	9 [3.5]	0	47 [2.8]	10 [3.0]	3 [6.5]
	Rhinitis	16 [1.7]	2 [1.0]	2 [0.9]	0	0	0	20 [1.2]	4 [1.2]	1 [2.2]
	Pharyngitis	7 [0.7]	0	0	0	2 [0.8]	0	9 [0.5]	2 [0.6]	0
	Cough	5 [0.5]	1 [0.5]	2 [0.9]	0	1 [0.4]	0	9 [0.5]	2 [0.6]	0
	Asthma	3 [0.3]	0	1 [0.5]	0	2 [0.8]	0	6 [0.4]	0	0
	Dyspnea	2 [0.2]	0	2 [0.9]	0	1 [0.4]	0	5 [0.3]	2 [0.6]	1 [2.2]
Skin & Appendages	Any event	20 [2.1]	3 [1.5]	9 [4.1]	0	7 [2.7]	0	39 [2.3]	13 [4.0]	3 [6.5]
	Rash	6 [0.6]	1 [0.5]	4 [1.8]	0	4 [1.6]	0	15 [0.9]	7 [2.1]	3 [6.5]
	Pruritus	4 [0.4]	1 [0.5]	1 [0.5]	0	3 [1.2]	0	9 [0.5]	3 [0.9]	0
	Sweat	5 [0.5]	1 [0.5]	1 [0.5]	0	0	0	7 [0.4]	2 [0.6]	0
	Rash vesic bull	1 [0.1]	0	2 [0.9]	0	0	0	3 [0.2]	0	0
	Urticaria	2 [0.2]	1 [0.5]	0	0	0	0	3 [0.2]	2 [0.6]	0
	App. Site React.	0	0	1 [0.5]	0	1 [0.4]	0	2 [0.1]	0	0
	Eryth. Multiform	1 [0.1]	1 [0.5]	0	0	0	0	2 [0.1]	0	0
Special Senses	Any event	53 [5.5]	12 [6.0]	13 [5.9]	1 [4.5]	31 [12.1]	1-25	111 [6.7]	20 [6.1]	5 [10.9]
	Taste perversion	42 [4.4]	12 [6.0]	12 [5.4]	1 [4.5]	28 [10.9]	0	95 [5.7]	16 [4.9]	2 [4.3]
	Parosmia	6 [0.6]	0	2 [0.9]	0	4 [1.6]	1-25	13 [0.8]	3 [0.9]	1[2.2]
Urogenital	Any event	8 [0.8]	0	1 [0.5]	0	2 [0.8]	0	11 [0.7]	2 [0.6]	1 [2.2]
	Urin. Abnorm.	0	0	1 [0.5]	0	1 [0.4]	0	2 [0.1]	0	0

*~ Reviewer's comment: The order of the adverse events has been shown from the most common to the least common. Adverse events if less than 0.5% (unless felt relevant or important) have not been tabulated. @ This does not concur given that there were three patients who experienced this AE only in the 0.1 mmol/kg dose group.
Some of the values have been rounded off to the next higher tenth decimal

160 file

MEMORANDUM OF TELEPHONE CALL
Between FDA and Sponsor

Date: March 2, 1999

APPLICATION NUMBER: N 20-937

Drug Name: Optimark

Name(Sponsor): Mallinckrodt (Mary Hamilton)
(314) 654-3272

AND

Name(FDA): James Moore, Project Manager, HFD-160
(301) 827-7510

Subject: Telephone Call Discuss if Fax with Clinical Proposal Received

Mary Hamilton called and inquired if the original fax and an additional page of a proposal to revaluate EKGs had been received and I told her it had been received. Ms. Hamilton also inquired if Dr. Raman(clinical reviewer) had any comments on what had been submitted thus far. I commented that he was not in today and I would speak to him on Wednesday or Thursday and inquire what his impression of the submitted material was. Ms Hamilton stated that her firm is anxious to have a yea or nay on the proposal so that they may begin the work. I conveyed that as soon as I spoke to Dr. Raman I would relay his impressions to the firm. She asked if that could be done by the end of the week and I said I would try to do that.

/S/
James Moore
Project Manager, HFD-160

CC: Moore HFD 160

HFD-160/Div File

MEMORANDUM OF TELEPHONE CALL
Between FDA and Sponsor

Date: January 26, 1999

APPLICATION NUMBER: N 20-937

Drug Name: Optimark

Name(Sponsor): Mallinckrodt-Mary Hamilton
St. Louis, Mo (314) 654-3272

AND

Name(FDA): James Moore

Subject: Scheduling Meeting to Discuss Chemistry Issues, Clinical Issues in NA Letter of December 23, 1998

At about 2:30pm January 26, 1999, I contacted Ms. Mary Hamilton of Mallinckrodt and informed her that FDA planned to schedule a T-Con for the week of February 15, 1999 to discuss chemistry issues detailed in the NA letter of December 23, 1998. Would this be acceptable to Mallinckrodt, I inquired?. I also mentioned that after the internal review of the proposal for the clinical section has been completed, I would telephone her and schedule a time for a T-Con to discuss the clinical issues from the NA letter. Ms. Hamilton assured me that the Sponsor would be available for a T-Con to discuss the chemistry issues any day of the third week of February.

Ms. Hamilton stated that she hoped that the T-Con to discuss the clinical issues could occur before the third week of February. I concurred and stated that was my hope as well. However, I emphasized that the scheduling of the T-Con to discuss clinical issues was dependent on the date of completion of the internal review of the clinical proposal. Ms. Hamilton conveyed that the reanalysis of the EKG data had already begun and that if the reanalysis was not in accordance with the requirements of FDA that they would have wasted time and effort performing the analysis. That is why it is very important that the t-con to discuss the clinical issues occur as soon as possible according to Ms. Hamilton. The exchange was polite and cordial.

James Moore
Project Manager, HFD-160

cc:HFD-160/moore

HFD-160/Div file

MEMORANDUM OF TELEPHONE CALL
Between FDA and Sponsor

Date: January 21, 1999

APPLICATION NUMBER: N 20,937

Drug Name: Optimark

Name(Sponsor): Mallinckrodt-Mary Hamilton

AND

Name(FDA): James Moore, Project Manager, HFD-160

Subject: Scheduling of Meeting on Clinical and Chemistry Issues from NA Letter

Today I spoke to Mary Hamilton, Manager Regulatory Affairs, Mallinckrodt, regarding review of two proposals and questions sent to FDA by her firm in response to clinical and chemistry deficiencies detailed in the NA letter of December 23, 1998. Ms. Hamilton inquired if the chemist and clincial reviewer assigned to Optimark have reviewed the proposals and questions submitted by her firm. She also asked if she could speak directly to Dr. Place, Chemistry Reviewer, regarding the chemistry issues and I said that Dr. Place would simply refer her to me if he was telephoned.

I explained that this is a very busy time for the reviewer staff and that each of them is being pulled in a number of different directions to perform required tasks. I said there is too much work and not enough personnel to perform all the required tasks in the time allotted. She said that Dr. Wolfangel had contacted Mr. R.K. Leedham, Supervisory Project Manager, regarding this matter earlier this month and asked if that was okay to do. I said it was but it would be better to contact me directly because I'm the project manager and I'm closer to the application than anyone else.

I stated that as soon as I have definitive word on a completed review of the proposals, I would inform her of that by telephone and discuss scheduling a t-con with her firm.

The call ended amicably and she thanked me for my efforts in trying to schedule a t-con.

160/ Dw file

MEMORANDUM OF TELEPHONE CALL
Between FDA and Sponsor

Date: January 5, 1999

APPLICATION NUMBER: N 20,937

Drug Name: Optimark

Name(Sponsor): Mallinckdrodt, Mary Hamilton

AND

Name(FDA): James Moore, Project Manager, HFD-160

Subject: Discussion of Issuing related to NA for Optimark

On January 5, 1999 I received a call from Mary Hamilton of Mallindkrodt requesting a T-con to discuss the clinical issues and the PK issues cited in the NA letter of December 23, 1998. I informed Ms. Hamilton that I would speak to the members of the division to ascertain appropriate scheduling of a T-con. I suggested that we meet via telecon and discuss all issues addressed in the NA letter at once. Ms. Hamilton said that the PK contact at her firm would ~~be~~ only be available on Wednesday and Thursday of this week and that a separate meeting with the pharmacokinetics reviewer would be best. She inquired who the pharmacokinetics reviewer was and I informed her that it was Dr. Young-Moon Choi.

I stated that I would get back to her regarding the schedule of a t-con to discuss the particular areas of interest addressed in the letter. The call ended amicably.

Later that day I telephone Ms. Hamilton and informed her that her firm should prepare specific questions regarding the NA letter, fax them to us and after the review of the specific questions posed a t-con could be scheduled. Ms. Hamilton said that the questions were really ones of clarification regarding the Pharmacokinetics issues and the clinical issues but she would prepare the questions and fax them to me by Thursday January 7, 1998.

This memo of t-con was prepared by James Moore, project manager.

c:\wpfiles\optimark.tcl

cc:NDA Division File 20-937

160 / Rev file

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE January 4, 1999
About 10:00AM I received a call from Dr. Pierro in which greetings and general personal comments were exchanged then followed by reference to the non-approval of this NDA. Dr. Pierro wanted to establish what the Agency wanted for the sponsor's reply to the clinical issues and in particular the EKG data. I noted that the reference standards for the PR, QRS, and QT intervals were in part an issue but that I could not discuss the clinical issues at the time of this call. I thought that it might be possible to FAX the EKG intervals and some informal guidance on assessing EKGs but felt it would be better if I had our CSO set up any necessary arrangements by telephone or a meeting to address the sponsor's issues. Dr. Pierro assured me that he was seeking specific feedback in order to provide the Agency a timely and comprehensive response.	NDA NUMBER 20-937 IND NUMBER TELECON/MEETING INITIATED BY [x] APPLICANT/ SPONSOR [ ] FDA MADE [X] BY TELEPHONE [ ] IN PERSON PRODUCT NAME Optimark FIRM NAME Mallinckrodt NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Joseph Pierro M. D. TELEPHONE unknown (
SIGNATURE /S/	DIVISION HFD-160