CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20937

APPROVAL LETTER

SEE ENTRY PACKAGE NDA 20937 FOR NDA 20975 AND NDA 20976

NDA 20-937
NDA 20-975
NDA 20-976

DEC 8 1999

Mallinckrodt, Inc.
Attention: Mary Hamilton
Manager, Regulatory Affairs
P.O. Box 5840
St. Louis, MO 63134

Dear Ms. Hamilton:

Please refer to your new drug applications (NDAs 20-937, 20-975, 20-976) dated February 28, 1998, received March 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OptiMark® (gadoversetamide) Injection. NDA 20-937 provides for the drug product in a glass vial; NDA 20-975 provides for the drug product in a pharmacy bulk pack, and NDA 20-976 provides for the drug product in a plastic syringe.

We acknowledge receipt of your submissions dated February 24, June 7, July 16, September 24, October 29, 30, and November 24, 1999, December 2, and December 6, 1999.

This new drug application provides for the use of OptiMARK (gadoversetamide) Injection with magnetic resonance imaging (MRI) in patients with an abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues; and with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities identified on computerized tomography.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDAs 20-937, NDA 20-975 and NDA 20-976." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated December 6, 1999. These commitments, along with any completion dates agreed upon, are listed below. Specifically, you have committed to conduct the following:

1. Pre-clinical cardiac electrophysiologic studies: These studies will evaluate action potentials and electrophysiologic channel blocking in appropriate animal models. A wide range of doses will be studied to provide an adequate margin of safety based on body surface area conversion.
2. Expanded clinical electrocardiographic monitoring: These studies will be conducted over a wide range of gadoversetamide doses. All patients will have continuous, comprehensive electrocardiographic monitoring.

You have committed to submitting the draft protocols within 3 months of OptiMark approval. Also, you committed to making all reasonable efforts to submit the completed studies within one year of OptiMark approval. The protocols for the studies should be submitted for review and comment before implementation.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note the format for pediatric studies is

Currently marketed gadolinium contrast agents are approved for use in pediatric patients over two years of age.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact James Moore, R.Ph., M.A., Project Manager, at (301) 827-7510.

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research