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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

Tyco/Mallinckrodt Health Care
Attention: Edward R. Porter
Manager, Regulatory Affairs
P.O. Box 5840
St. Louis, MO 63134

Dear Mr. Porter:

Please refer to your supplemental new drug application(s) dated March 29, 2002, received April 1, 2002, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for OptiMARK®, (gadoversetamide) Injection.

We acknowledge receipt of your submission(s) dated September 26, 2002, January 13 and 24, 2003. We also acknowledge receipt of facsimiles of January 30 and 31, 2003.

These supplemental new drug applications provide for use of OptiMARK® Injection with a Power Injector at a dose of 0.2mL/kg (0.1mmol/kg) at a rate of 1-2mL/sec.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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, these submissions should be designated "FPL for approved supplement NDA 20-937/20-975/20-976/S-003." Approval of these submissions by FDA is not required before the labeling is used.

We also remind you of your post-marketing study commitments in the approval letter dated December 8, 1999. These commitments are listed below.

In order to clarify whether gadoversetamide has a proarrhythmic effect, the following were requested:

1. Pre-clinical cardiac electrophysiologic studies. These studies should evaluate action potentials and electrophysiolic channel blocking 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 electrocardiographic monitoring: These studies should be conducted over a wide range of gadoversetamide doses. All patients should have continuous, comprehensive electrocardiographic monitoring.

In reference to commitment 2, we remind you of your additional commitment in the facsimile of January 30, 2003, to provide the results of the ECG clinical study report for protocol 1177-01-716 within 4 months of the date of issue of the action letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to

these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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. 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". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CAPT James Moore, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Patricia Y. Love, M.D., M.B.A.
Division Director
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

James Moore
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CSO