CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18467/S13

APPROVAL LETTER

DIV

NDA 18-467/S-013 & 014

DEC 29 1993

The Du Pont Merck Pharmaceutical Company
Radiopharmaceutical Division
331 Treble Cove Road
North Billerica, Massachusetts

Attention: Laura A. Lee
Sr. Regulatory Affairs Associate

Dear Ms. Lee:

Reference is made to your supplemental new drug applications dated July 26, 1991 (S-013), and April 4, 1992 (S-014), submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hepatolite, Kit for the Preparation of Technetium Tc 99m Disofenin.

Supplement 013 provides for revisions to the package insert to include radiation dosimetry tables for jaundiced patients with malignant obstructive disease. Supplement 014 provides for the diagnosis and evaluation of acute cholecystitis when performed with morphine sulfate augmentation. We note that, as requested in our April 13, 1993, approvable letter, the indication allowing for the diagnosis and evaluation of

has been withdrawn from S-014 in your amendment dated August 6, 1993.

We also acknowledge receipt of your correspondence and amendments dated April 9 and 21(2), May 13, August 6(2), November 23, and December 17, 1993.

We have completed the review of these applications including the submitted draft labeling dated December 16, 1993. The applications are approved, as amended, effective as of the date of this letter.

Please submit twelve copies of the final printed labeling (FPL) as soon as it is available. Seven of the copies should be individually mounted on heavyweight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 18-467/S-013 & S-014". Approval of the submission by FDA is not required before the labeling is used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

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

If you have any questions regarding this communications, please contact Ms. Susan Lange (301) 443-5818.

Sincerely yours.

/S/

Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

cc: NDA Arch.
HFD-160
HF-2 w/labeling
HFC-130/Dist Off. w/ labeling
HFD-80/ w/ labeling
HFD-100/ w/ labeling
HFD-600/ w/ labeling
HFD-730/ w/ labeling
HFD-161/Lange
F/T by: AChapman-12-14-93 N18467.SS
SUPPLEMENT APPROVAL

12/22/93

APR 13 1993

NDA 18-467/S-014

The Du Pont Merck Pharmaceutical Company
Radiopharmaceutical Division
331 Treble Cove Road
North Billerica, Massachusetts 01862

Attention: Thomas J. Mullins
Manager, Regulatory Affairs

Dear Mr. Mullins:

Reference is made to your supplemental new drug application dated April 8, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hepatolite, Kit for the Preparation of Technetium Tc99m Disofenin.

The supplement provides for two new clinical indications:

1. The diagnosis and evaluation of acute cholecystitis when performed with morphine sulfate augmentation.

2. The diagnosis and evaluation of [redacted]

We have completed our review of this supplemental application including the submitted draft labeling dated April 8, 1992, and it is approvable for the diagnosis and evaluation of acute cholecystytitis when performed with morphine augmentation. Before the application may be approved for this indication, we request that you submit the following revisions to the draft labeling as an amendment to this application:

1. Under the **Indications** section, paragraph 3, which begins "Hepatolite^{R} Kit for the preparation of [redacted]" should be deleted and the following paragraphs added:

   "When the gall bladder fails to appear within the first 60 minutes of imaging after the administration of Hepatolite, a single 0.04 mg/kg dose of intravenous morphine, diluted in 10 mL normal saline and administered over 3 minutes, has been reported to be effective in shortening the 4 hours usually required for observations, to 90 minutes. In patients who do not have acute cholecystitis, the use of morphine has been reported to result in visualization of the gall bladder within an additional 30 minutes.

False negative visualization of the gallbladder in cases of acute cholecystitis, and false positive failure of a normal gallbladder to visualize have been reported with both morphine augmentation and the standard 4 hours of observation."

2. Under the **Indications** section, paragraph 5, which begins

should be deleted.

3. Under the **Precautions** section, please add the following:

"In cases where there has been no visualization of the gallbladder after 60 minutes of scanning, morphine should be carefully administered provided there is no contraindication to the use of narcotics. There should be clear evidence of patency of the common duct, such as observed entry of radiopharmaceutical into the small bowel, prior to the administration of morphine to such patients.

Morphine augmentation has not been associated with any serious adverse events in the reported cases, but the administration of morphine in biliary colic may increase patient discomfort, and the recommended dose of 0.04 mg/kg (2-4 mg) may be associated with significant respiratory depression and/or postural syncope in vulnerable patients. Facilities using morphine augmentation should be able to monitor patients for the adverse effects of narcotics and have the means at hand to manage them, including the ready availability of a specific narcotic antagonist such as naloxone."

The supplement is not approvable for the diagnosis and evaluation of

The application fails to provide information for this new indication as required under section 505(d) of the Act and 21 CFR 314.125(b) of the FDA's implementing regulations as follows:

Substantial evidence has not been presented to establish as an effective diagnostic test. The information used to support this new clinical indication is insufficient regarding dose, range of patient population studied, ejection fraction percentage chosen to distinguish normal and abnormal, test sensitivity, and tissue specificity.

We request that you submit an amendment to the supplemental application withdrawing this indication.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw the supplemental application. The changes indicated above cannot be legally implemented until you have been notified in writing that the application is approved.

Should there be any questions regarding this communication, please contact Susan Lange, Consumer Safety Officer at (301) 443-5818.

Sincerely yours,

/S/ M.D. M.D.

Paula Botstein, M.D.
Acting Director
Division of Medical Imaging
Surgical and Dental Drug Products
and
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: NDA 18-467/S-014
HFD-160/DivFile
HFD-130/Allen/
HFD-80/
HFD-160/Jones/Chacalos
HFD-180/Freed
HFD-007/Wright
HFD-160/Botstein
HFD-161/McCort/Lange

Acknowledgements: Jones-03-15-93/Lange-03-15-93/Cheever-03-11-93
F/T by: AChapman 04-12-93
SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18467/S13

APPROVABLE LETTER

NDA 18-467/S-013

APR - 2 1993

The DuPont Merck Pharmaceutical Company
Radiopharmaceutical Division
331 Treble Cove Road
North Billerica, Massachusetts 01862

Attention: Michelle E. Foster, Ph.D.
Regulatory Affairs Scientist

Dear Dr. Foster:

Reference is made to your supplemental new drug application dated July 26, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hepatolite, Kit for the Preparation of Technetium Tc99m Disofenin.

This supplement provides for revisions in the labeling to include radiation dosimetries to jaundiced patients with malignant obstructive disease.

We have completed our review of this supplemental application including the submitting labeling, and it is approvable. Before the application may be approved, however, we request that you submit the following labeling revisions as an amendment to this supplement:

1. The following statement should be added to the **ADVERSE REACTIONS** section in response to submitted ADR reports:

   "Infrequently, death has been reported in association with the use of this class of agents."

2. In the **PRECAUTIONS** section of the package insert, **General** subsection, the following statement:

   should be revised as follows:

   "Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides."

3. In the **Pregnancy** subsection, the following statement should be deleted:

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under CFR 314.110. In the absence of such action FDA may take action to withdraw the application. The changes indicated above cannot be legally implemented until you have been notified in writing that the application is approved.

Should there be any questions regarding this communication, please contact Susan Lange, at (301) 443-5973.

Sincerely yours,

/S/ MD 4/1/93

Paula Botstein, M.D.
Acting Director
Division of Medical Imaging
Surgical and Dental Drug Products
and
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: NDA 18-467/S-013 Acknowledgements: SMO/Jones/SCSO/Cheever
HFD-160/DivFile
HFD-130/Allen/ w labeling
HFD-80 /w labeling
HFD-160/DivDir/Botstein
HFD-160/SMO/Jones
HFD-160/MO/Chacalos
HFD-160/SChem/Sheinin
HFD-160/SPharm/DeWitt
HFD-161/CSO/Lange
HFD-161/CSO/McCort
McCort 3/8/93
Acknowledgements: Jones-03-23-93/Cheever-03-11-93/
Chacalos-03-16-93
F/T by: AChapman 03-31-93
SUPPLEMENT APPROVABLE

3/31/93