CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020607

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-607

G.D. Searle & Company
Attention: Peter East
4901 Searle Parkway
Skokie, Illinois 60077

DEC 24 1997

Dear Mr. East:

Please refer to your new drug application dated December 22, 1995, received December 26, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec (diclofenac sodium/misoprostol) Tablets.

We acknowledge receipt of your submissions dated September 3, September 5, September 10, September 19, September 29, October 1, October 14, October 16, November 4, and November 20, 1997. The user fee goal date for this application is April 15, 1998.

This new drug application provides for a fixed combination drug product for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at high risk for developing NSAID-induced gastric and duodenal ulcers and their complications.

We have completed the review of this application, including the submitted draft labeling, 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 enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling 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 "FINAL PRINTED LABELING" for approved NDA 20-607. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated

Please implement these changes as soon as possible. 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.

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, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

APPROVABLE LETTER

NDA 20-607

SEP 17 [illegible]

G.D. Searle & Company
Attention: Peter East
4901 Skokie Parkway
Skokie, Illinois 60077

Dear Mr. East:

Please refer to your new drug application dated December 22, 1995, received December 26, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec (diclofenac sodium/misoprostol) Tablets.

We acknowledge receipt of your submissions dated February 3, March 5, March 19, May 8, June 18, July 8, August 4, and August 22, 1997. The User Fee goal date for this application is November 9, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit a satisfactory response to the following items:

Chemistry, Manufacturing, and Controls:

I. Method of Manufacture

A.

B.

Provide the which were employed in

C. Tests

The misoprostol

misoprostol. Provide for a and specification based upon your manufacturing history. You may propose a plan for reducing the number of samples tested after you demonstrate on the appropriate number of production batches that this test and specification is consistently met. In a supplement requiring Agency approval prior to implementation, please submit this plan, identifying the number of batches to be tested and your sampling plan.

II. Stability

A. Expiration Date

To date, you have submitted stability data of This is insufficient to support the proposed three (3) year expiration date. Please submit additional 25°C stability data, which you have said is complete though 2 years, along with statistical analysis.

B. Misoprostol

Your one (1) year stability data, in all proposed indicate that the the following limits (see data below):

Propose and justify revised impurity limits for individual and total based upon your two year stability data

C. Stability Protocol-Extension of Expiration Dating

You have committed to performing the for diclofenac sodium in your market stability program. Amend your stability protocol for extension of expiry to include this test.

D. Stability Protocol- Annual Market Batch Protocol

Add the for diclofenac sodium to your annual market batch stability protocol as you have committed to do.

III. Methods Validation

Submit three (3) copies of your revised methods validation package which

diclofenac sodium.

Final Printed Labeling:

In addition, it will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1.

2.

3.

4.

5.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 9-16-97

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Enclosure: Draft Labeling

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-607
HFD-180/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-180/B.Strongin
HFD-180/K.Robie-Suh
HFD-180/J.Choudary
HFD-180/G.Young
HFD-180/E.Duffy
HFD-180/G.Chen
HFD-550/J.Hyde
HFD-550/J.Witter
HFD-550/L.LoBianco
HFD-720/M.Huque
HFD-720/M.Fan
HFD-850/L.Lesko
HFD-870/M.L.Chen
HFD-870/L.Kaus
HFD-103/Office Director
HFD-105/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)

APPEARS THIS WAY
ON ORIGINAL

/S/ 9-16-97

Drafted by: BS/September 5, 1997/c:\wpfiles\n\20607709.0
Initialed by: EPD/September 5, 1997
KRS/September 8, 1997
PB/September 11, 1997
Final: BS/September 16, 1997

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL