CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

CORRESPONDENCE

NDA 20-607

MAR 26 1997

G.D. Searle & Company
Attention: Peter East
4901 Searle 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 for the acute and chronic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) in patients at risk of developing NSAID-induced gastric ulcers and their complications.

We acknowledge receipt of your submissions dated February 5 and 23, March 4, 8 and 21, May 9 and 23, June 27, and December 17 and 20 1996, January 22, and February 11, and 18, 1997. The original User Fee goal date for this application was December 26, 1996. Your submission of December 17, 1996 extended the User Fee goal date to March 26, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

I. Clinical And Statistical

A. The Diclofenac Component

The

To establish the efficacy of the diclofenac in the Arthrotec formulations proposed for marketing, adequate and well-controlled clinical studies providing substantial evidence of safety and efficacy or data that demonstrate bioequivalence

The submitted clinical studies of Arthrotec in the treatment of RA were not adequate to provide substantial evidence of the safety and efficacy of the drug in this condition. The principal efficacy study (NN2-95-ST-352) failed to demonstrate that diclofenac 75 mg B.I.D., diclofenac 50 mg/misoprostol 200 μg T.I.D., or diclofenac 75 mg/misoprostol 200 μg B.I.D was clinically superior to placebo. In this randomized, double-blind, placebo-controlled trial, Arthrotec 75 was shown superior to placebo for three out of four efficacy parameters at week six, but only two out of four parameters at week twelve. Arthrotec 50 failed to beat placebo on any of the primary variables at the week six time point and was shown to be statistically superior to placebo at the week twelve time point for only one out of four efficacy parameters. To

demonstrate efficacy in rheumatoid arthritis at least three out of the four primary efficacy variables must consistently be statistically significantly better for the NSAID compared to placebo.

The use of Arthrotec in the treatment of OA is supported principally by one study (NN2-94-02-349), a randomized, double-blind, placebo-controlled study in which the efficacy of diclofenac 75 mg B.I.D. was equivalent to diclofenac 50 mg/misoprostol 200 μg T.I.D. and diclofenac 75 mg/misoprostol 200 μg B.I.D.. Questions about the adequacy of the randomization in this trial were raised due to an unequal distribution of patients between groups, and would need to be addressed satisfactorily before this study could be considered adequate. The submitted studies are not sufficient to support comparative claims between Arthrotec and either piroxicam or naproxen.

In addition, due to the following flaws in its design and conduct, the data from Study 013 does not change the assessments noted above:

1. the lack of statistically significant differences is not evidence of equivalence;

2. the lack of "traditional disease specific" endpoints such as tender and swollen joint counts in RA or target joints in OA, as well as the study design and analysis methodology, make it hard to claim substantial evidence of safety and efficacy.

B. The Misoprostol Component

While evidence from both Cytotec and Arthrotec studies are cited to support efficacy, bioequivalence of the Arthrotec formulation to be marketed to marketed Cytotec must be demonstrated to qualify the Cytotec studies in support of the Arthrotec NDA.

We note that you have requested that Arthrotec be indicated only for the prevention of gastric ulcers, and not duodenal ulcers at this time. We view inclusion in the labeling of information about duodenal ulcer prevention as providing important safety information. In NSAID induced duodenal ulcer prevention, two Cytotec studies clearly establish the benefit of the 200 μg Q.I.D. dose regimen (studies 053 and 041). In no case was that regimen studied without effectiveness. On the other hand, the 200 μg B.I.D. dose regimen was significantly effective in one study (053) and not in three others (551, 136, and 349). The T.I.D. dose was also effective in one Cytotec study (053), but not in two others (296 and 349), both Arthrotec Studies.

Study 013 suffers from major deficiencies of design and execution that make it unacceptable as an adequate and well-controlled study for evaluation of misoprostol efficacy. There was no baseline endoscopy to document absence of ulcers in patients at study entry. Endoscopy was done only at study completion. Also, study blinding may have been compromised because the appearance of the Arthrotec tablets was clearly different (size, shape, color, and embossing) from that of diclofenac tablets.

An overview of individual studies in which effectiveness in various dose regimens in gastric ulcer and duodenal ulcer prevention is provided by the following chart.

Dosing Regimen		Gastric Ulcer	Duodenal Ulcer
200 μg	Q.I.D.	Study 053 Study 002 Study 003	Study 053 Study 041
	T.I.D.	Study 053* Study 320	Study 053
	B.I.D.	Study 053	Study 053
100 μg Q.I.D.		Study 002S**	----------

* misoprostol 200 mcg T.I.D. was therapeutically equivalent to misoprostol 200 mcg Q.I.D.
** misoprostol 200 mcg Q.I.D. was superior to 100 mcg Q.I.D.

From the point of view of dose selection for the misoprostol component, assuming bioequivalence of the Arthrotec formulations to marketed Cytotec, the Q.I.D. regimen appears best, but not well tolerated. The T.I.D. regimen is equivalent for gastric ulcer (GU) prophylaxis, not yet established for duodenal ulcer (DU) prophylaxis, and well tolerated. Equivalent efficacy of the B.I.D. regimen to Q.I.D. and T.I.D. for GU prophylaxis was not demonstrated, and data have not been provided to demonstrate the efficacy of a B.I.D. or T.I.D. regimen for DU prophylaxis.

II. Bioequivalence

A. Arthrotec 50

Diclofenac contained in the Arthrotec 50 formulation to be marketed was shown to be bioequivalent alone in terms of diclofenac AUC and C_{max}. This was an indirect link.

Misoprostol in the Arthrotec 50 formulation to be marketed was shown to be bioequivalent to the marketed Cytotec alone for misoprostol acid AUC, but not for misoprostol acid C_{max}. This was also an indirect link.

B. Arthrotec 75

Diclofenac in the Arthrotec 75 formulation to be marketed was shown to be bioequivalent to the marketed Voltaren 75 mg tablet alone for diclofenac AUC, but not for diclofenac C_{max} after single or multiple dosing.

Misoprostol in the Arthrotec 75 formulation to be marketed was shown to be bioequivalent to the marketed Cytotec alone for misoprostol AUC, but not for misoprostol C_{max}.

Therefore, bioequivalence was only demonstrated, indirectly, for the diclofenac component in the Arthrotec 50 formulation to be marketed. Bioequivalence to Cytotec was not demonstrated for the misoprostol component in either the Arthrotec 50 or Arthrotec 75 formulation to be marketed.

III. The Fixed Combination Product

For the proposed Arthrotec 50 and Arthrotec 75 formulations, 50 mg and 75 mg diclofenac are provided in each tablet respectively. Two hundred micrograms of misoprostol are present in each tablet as well. With a dose regimen of 100 - 200 mg (or 225 mg) of diclofenac possible for the treatment of OA and RA as per the Voltaren labeling, it is not clear that the proposed formulations of Arthrotec without additional misoprostol would provide adequate protection against NSAID induced peptic ulcer disease for a significant portion of the target patient population i.e., those with OA and RA at high risk of serious complications.

Only those OA patients taking 150 mg diclofenac (three Arthrotec 50 tablets) daily would receive the 200μg T.I.D. dose, but not those patients requiring the 100 mg diclofenac daily. No patient with OA would receive the 200μg Q.I.D. dose.

For RA patients, those who would take Arthrotec three times a day (giving 150 mg or 225 mg of diclofenac) would receive an effective dose, 200 μg T.I.D. of misoprostol, for the prevention of gastric ulcers, but not duodenal ulcers.

Arthrotec 50 or Arthrotec 75 taken B.I.D can provide only misoprostol 200 μg B.I.D., a dose not shown as effective as higher doses. It is conceivable that this low dose of misoprostol might be useful for patients unable to tolerate higher doses.

Neither tolerability nor individualization of diclofenac dosing considerations add sufficiently to the utility of the fixed combination Arthrotec formulations as now stated in the draft labeling. Lowering the diclofenac dose for a given patient with RA or OA would provide less ulcer protection than might be possible and tolerated with use of the single diclofenac and misoprostol drug products.

It is probable that physicians will prescribe Arthrotec according to the amount of diclofenac needed by the patient, taking whatever misoprostol dose is provided in the formulation. With the results of the MUCOSA study indicating that Cytotec does prevent serious ulcer complications, the fragility of the patient population at risk of such complications, and the currently available dose response database, we are concerned that these fixed dose formulations may not provide an adequate Cytotec dose.

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 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Gastrointestinal and Coagulation Drug Products to discuss what further steps need to be taken before the application may be approved.

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

Sincerely yours,

/S/ 3/24/97

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-607
HFD-180/Div. files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
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/W.Chambers
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-870/H.R.Choi

Drafted by: BS/March 6, 1997, March 7, 1997/c:\wpfiles\n\20607703.0
Initialed by: L.Kaus/March 25, 1997
K.Robie-Suh/March 26, 1997
final: BS/March 26, 1997

NOT APPROVABLE (NA)

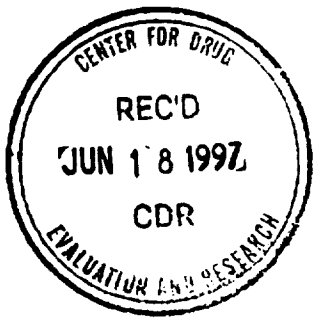
/S/ 3-26-97

APPEARS THIS WAY
ON ORIGINAL

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

PATENT INFORMATION

June 17, 1997



Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 20-607 Arthrotec®
(diclofenac Na/misoprotsol)

SEARLE

Gentlemen:

In accordance with Section 21 CFR 314.53(d)(4) Searle submits this revised Patent Statement for NDA 20-607, Arthrotec®.

Please direct any questions or comments concerning this submission to the undersigned.

Sincerely,

Peter F. East

Peter F. East
Associate Director,
Regulatory Affairs
(847) 982-8606
(847) 982-8152 fax

PFE/br
Enclosures

Strongin

NDA 20-607

G.D. Searle & Company
Attention: Eva Essig, Ph.D.
4901 Searle Parkway
Skokie, Illinois 60077

MAY - 6 1996

Dear Ms. Essig:

Please refer to your New Drug Application submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec Tablets.

We also refer to our letter dated April 15, 1996 in which we stated that we had completed the review of your proposed tradename, Arthrotec, and recommended against its use. Finally, we refer to your subsequent telephone conversation regarding this issue with the Chairman of the Labeling and Nomenclature Committee, Dan Boring, Ph.D.

We have reevaluated our decision, and have now determined that the tradename Arthrotec is acceptable.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
NDA 20-607
HFD-180
HFD-180/Reviewers
HFD-180/CSO/B.Strongin
HFD-550/R.Neuner
HFD-550/CSO/L.Lobianco
R/D Init: S.Fredd/May 3, 1996
BS/May 3, 1996
BS/May 3, 1996/c:\wpfiles\n\20607605.0

/S/ 5-3-96

ADVICE

/S/ 5/6/96

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Strongin

NDA 20-607

G.D. Searle & Company
Attention: Eva Essig, Ph.D.
4901 Searle Parkway
Skokie, Illinois 60077

APR 15 1998

Dear Dr. Essig:

Please refer to your New Drug Application submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec Tablets.

We have completed the review of your proposed tradename, Arthrotec, and have concluded that there is a potential for confusing it with the medical term "arthritic" and with the tradename for the newly approved product Amphotec. In addition, it is recommended that an indication not be included in a proposed tradename. For these reasons, we recommend against its use.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
NDA 20-607
HFD-180
HFD-180/Reviewers
HFD-180/CSO/B. Strongin
HFD-550/R. Neuner
HFD-550/CSO/L. Lobianco
R/D Init: S. Fredd/April 10, 1996
BS/April 10, 1996
BS/April 12, 1996/c:\wpfiles\n\20607604.n

/S/ 4/12/96

ADVICE

/S/ 4/12/96

APPEARS THIS WAY
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APPEARS THIS WAY
ON ORIGINAL

Strongin

NDA 20-607

MAY 23 1997

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

Dear Mr. East:

Please refer to your new drug application for Arthrotec (diclofenac sodium/misoprostol) Tablets.

In response to your telephone request of May 9, 1997, we have enclosed the Statistical Review and Evaluation dated September 11, 1996. We will forward the remaining statistical reviews as soon as possible.

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

Sincerely yours,

/S/ 5-22-97

APPEARS THIS WAY
ON ORIGINAL

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

enclosure

APPEARS THIS WAY

enclosed documents:
Statistical Review and Evaluation dated September 11, 1996

cc:
Original NDA 20-607
HFD-180/Div. Files
HFD-180/CSO/B.Strongin
HFD-720/M.Huque
HFD-720/M.Fan

/S/ May 22, 1997

Drafted by: BS/May 22, 1997/c:\wpfiles\n\20607705.1
final: LT/May 22, 1997

GENERAL CORRESPONDENCE

Strongin

NDA 20-607

MAY - 6 1997

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

Dear Mr. East:

Please refer to your new drug application for Arthrotec (diclofenac sodium/misoprostol) Tablets.

In response to your telephone request of March 31, 1997, we have enclosed the Clinical Pharmacology and Biopharmaceutics Reviews dated October 31, 1996 and February 24, 1997.

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

Sincerely yours,

/S/ 5-6-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

enclosure

enclosed documents:
Clinical Pharmacology and Biopharmaceutics Reviews dated October 31, 1996 and February 24, 1997

cc:
Original NDA 20-607
HFD-180/Div. Files
HFD-180/CSO/B.Strongin
HFD-180/K.Robie-suh

/S/ 5-5-97

Drafted by: BS/May 5, 1997/c:\wpfiles\n\20607705.0
final: LT/May 5, 1997

GENERAL CORRESPONDENCE

NDA 20-607

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

APR 18 1997

Dear Mr. East:

Please refer to your new drug application for Arthrotec (diclofenac sodium/misoprostol) Tablets.

In response to your telephone request of March 31, 1997, we have enclosed the Medical Officer's reviews and the Division Director's Memo from the Division of Gastrointestinal and Coagulation Drug Products, and the Medical Officer's Consult Reviews from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products.

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

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

enclosure

enclosed documents:
Medical Officer's Reviews -
Dr. Kathy Robie-Suh dated: December 5, 1996 and March 7, 1997
Amendment to Medical Officer's Review
Dr. Kathy Robie-Suh dated: April 7, 1997
Medical Officer's Consult Reviews from HFD-550-
Dr. Rosemarie Neuner dated December 10, 1996
Dr. James Witter dated February 28, 1997
Division Director's Memo
Dr. Stephen Fredd, dated December 9, 1996

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-607
HFD-180/Div. Files
HFD-180/CSO/B.Strongin
HFD-180/K.Robie-suh

/S/ 4/17/97

Drafted by: BS/April 17, 1997/c:\wpfiles\n\20607704.0
final:-SF/April 17, 1997

/S/ 4/18/97

GENERAL CORRESPONDENCE

8.1

NDA 20-607

- 9 1997

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

Dear Mr. East:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Arthrotec (diclofenac sodium/misoprostol) Tablets.

We also refer to the meeting between representatives of your firm and FDA on December 5, 1996. The following represents our summary of the meeting.

MEMORANDUM OF MEETING

Meeting Date:	December 5, 1996
Time:	4:30PM - 6:00PM
Location:	Conference Room K, Parklawn Building
Application:	NDA 20-607, Arthrotec (diclofenac sodium/misoprostol) Tablets
External Meeting Requester:	G.D. Searle & Company
Type of Meeting:	Discussion of the pending action for this NDA
Meeting Chair:	Paula Botstein, M.D., Acting Director, Office of Drug Evaluation III
Meeting Recorder:	Brian Strongin, Regulatory Health Project Manager

FDA Attendees, Titles and Office/Division:

Office of the Center Director

Murray Lumpkin, M.D.	Deputy Center Director for Review Management
Robert Temple, M.D.	Associate Director for Medical Policy

Office of Drug Evaluation III (HFD-103)

Paula Botstein, M.D.	Acting Director

Office of Drug Evaluation V (HFD-105)

Michael Weintraub, M.D.	Director

Division of Gastrointestinal and Coagulation Drug Products (HFD-180

Stephen Fredd, M.D.	Director
Kathy Robie-Suh, M.D., Ph.D.	Medical Officer
Eric Duffy, Ph.D.	Team Leader, Chemistry
George Chen, Ph.D.	Review Chemist
Brian Strongin	Regulatory Health Project Manager

Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550)

Wiley Chambers, M.D.	Acting Director
John Hyde, M.D.	Team Leader, Medical
Rosemarie Neuner, M.D.	Medical Officer
Lisante LoBianco	Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Nancy Smith, Ph.D.	Director
Milton Fan, Ph.D.	Mathematical Statistician

Division of Biometrics IV (HFD-725)

Hoi Leung, Ph.D.	Mathematical Statistician

Division of Biopharmaceutics (HFD-870)

Lydia Kaus, Ph.D.	Team Leader, Biopharmaceutics
Hae-Ryun Choi, Ph.D.	Biopharmaceutics Reviewer

Office of the Chief Counsel

Diane Maloney, Esquire	Staff Counsel

External Constituent Attendees and Titles:

G.D. Searle & Company

Robert Bogomolny, Esquire	Corporate Senior V.P., General Counsel
John Alexander, M.D.	Executive V.P., Clinical Research
Steve Geis, M.D.,Ph.D.	Executive Director, Clinical Research
Richard Spivey, Ph.D.	V.P., Worldwide Regulatory Affairs
Tomas Bocanegra, M.D.	Senior Director, Clinical Research
Janice Toran	Assistant General Counsel

Consultants

Geoffrey Levitt, Esquire
James Lewis, M.D.

Background:

This application was submitted December 22, 1995 for the acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in patients at risk of NSAID-induced gastroduodenal ulcers. Arthrotec Tablets contain either 50mg or 75mg of diclofenac sodium in an enteric-coated core surrounded by a mantle containing 200μg of misoprostol. Ciba-Geigy's Voltaren brand of diclofenac sodium (NDA 19-201) has been approved for the acute and chronic treatment of the signs and symptoms of OA, RA and ankylosing spondylitis since July 28, 1988. The currently approved dosage range for diclofenac is 100mg - 150mg/day for OA taken in QD, BID, or TID regimens, and 150mg - 200mg/day for RA taken in BID, TID, or QID regimens. G.D. Searle's Cytotec brand of misoprostol (NDA 19-268) has been approved at a 200 μg QID dosage for the prevention of NSAID-induced gastric ulcers in patients at high risk of complications from such ulcers since December 27, 1988. Cytotec efficacy supplement S-019 (submitted December 24, 1993) is approvable for a dosage of 200μg QID for the prevention of NSAID-induced duodenal ulcers with an alternative dosage of 200μg TID for the prevention of NSAID-induced gastric ulcers only in patients unable to tolerate the higher dose. In the DOSAGE AND ADMINISTRATION section of the Arthrotec draft labeling, Searle recommends taking one tablet two or three times per day, providing a dosage range of 100mg - 225mg/day of diclofenac sodium and 400μg - 600μg/day of misoprostol. The user fee due date for this application is December 26, 1996.

Objective:

To reach agreement with the Agency that:

1. Arthrotec is approvable in BID and TID doses for the treatment of the signs and

symptoms of OA and RA in patients at risk of NSAID-induced gastric ulcers based on existing data in the Arthrotec NDA and Cytotec efficacy supplement 019 (submitted December 24, 1993, approvable June 6, 1996).

2. Approvability of Arthrotec is not contingent upon resolution of all Cytotec SNDA issues.

3. Approvability is consistent with the Agency's policy regarding fixed-combination drug products.

Discussion Points:

1. G.D. Searle provided the following background information regarding Arthrotec:

   A. Arthrotec addresses a major public health issue (NSAID-induced peptic ulcers), and enhances compliance.

   B. Arthrotec is approved in 45 countries, including the U.K., Canada, Sweden, and Germany, with BID/TID as the recommended dosage regimen.

   C. Data from six pivotal trials, three in OA patients and three in RA patients, were included in the submission. Two of the OA trials and one RA trial utilized upper GI endoscopy to assess misoprostol efficacy, and one OA (Study 349)and one RA trial (Study 352) was conducted in the U.S. using a placebo control and patients whose arthritis was flared. The application includes data from 2453 patients.

2. G.D. Searle presented information in support of their view that misoprostol does not interfere with diclofenac's anti-arthritic efficacy:

   A. The incidence of withdrawal due to treatment failure in pivotal OA Study 349 was significantly lower for all active comparators (1.9% for diclofenac 75 mg BID, 1.3% for Arthrotec 50 TID and 2.3% for Arthrotec 75 BID)than placebo (15.4%).

   B. The incidence of withdrawal due to treatment failure in pivotal RA Study 352 was also significantly lower for all active comparators (14% for diclofenac 75mg BID, 15% for Arthrotec 50 TID, and 20.7% for Arthrotec 75 BID) than placebo (38.2%).

   C. G.D. Searle described Arthrotec as an NSAID for the treatment of OA and RA with an improved safety profile to diclofenac and dosed according to the approved diclofenac regimen.

3. Searle presented information comparing the incidence of withdrawal due to any adverse event and the incidence of withdrawal due to specific GI events for Arthrotec versus diclofenac and placebo in the Arthrotec fixed-combination trials. The incidences for diclofenac and Arthrotec were similar with both exceeding placebo.

4. The firm presented information from endoscopic studies in support of their statement that two adequate and well-controlled clinical studies support BID (200 μg BID of misoprostol) and TID (200 μg TID of misoprostol) Arthrotec to prevent NSAID-induced gastric ulcers:

   A. The firm noted that there were issues remaining related to Cytotec S-019, but stated their view that approvability of NDA 20-607 is not contingent upon resolution of all Cytotec S-019 issues. However, data in S-019, in the firm's view, support Arthrotec approvability. (Note: At a September 18, 1996 meeting with the Agency regarding S-019, the firm was told that Cytotec data may be used by reference in support of NDA 20-607 when relevant.)

   B. The firm presented data from Arthrotec Study 349 showing that the incidence of gastric ulcers was significantly less for Arthrotec 50 TID (3%), Arthrotec 75 BID (4%) and placebo (3%) than diclofenac 75 mg BID (11%).

   C. Cytotec Study 053 was a multicenter, parallel, placebo controlled, randomized, and double blind study that evaluated the efficacy and safety of oral Cytotec in 200μg BID, TID and QID for the prevention of NSAID-induced gastric and duodenal ulcers. The firm presented data from Study 053 showing that the incidence of gastric ulcers was significantly less for QID (3.1%), TID (3.2%), and BID (6.3%) Cytotec than placebo (11.2%). The TID and QID regimens though, appeared superior to the BID regimen.

5. It was the firm's contention that the Agency's combination drug policy is applicable to Arthrotec because diclofenac contributes anti-arthritic efficacy and misoprostol prevents NSAID-induced peptic ulcers, thus enhancing the safety of diclofenac, the primary active ingredient, and the combination is safe and effective at the proposed dosages.

Recommendations/Conclusions:

The Agency provided the following discussion, comments, and recommendations concerning the firm's contention that Arthrotec is approvable in BID and TID doses for the treatment of OA and RA in patients at risk of NSAID-induced gastric ulcers based on existing data from the Arthrotec NDA and Cytotec efficacy supplement S-019:

1. No decision regarding approvability could be made by the conclusion of the meeting

since the application was under review.

2. Since the diclofenac in the Arthrotec formulations proposed for marketing is not the approved diclofenac, Voltaren, adequate and well-controlled studies providing substantial evidence of the safety and efficacy of the diclofenac component or data that demonstrate bioequivalence to Voltaren must be provided. Since evidence from both Cytotec and Arthrotec studies are cited to support efficacy of the misoprostol component of Arthrotec, bioequivalence of the Arthrotec formulations proposed for marketing to Cytotec must be demonstrated to qualify the Cytotec studies in support of the Arthrotec NDA. The issues raised in the November 22, 1996 biopharmaceutics information request letter, particularly request number one asking the firm to, provide data from studies which directly compare the formulation of Arthrotec proposed for marketing to marketed Voltaren and Cytotec to demonstrate that diclofenac and misoprostol in the Arthrotec formulation proposed for marketing are bioequivalent to Voltaren and Cytotec, must be addressed. The response may be classified as a major amendment which would provide a three month extension to the user fee due date.

3. Dr. Neuner summarized the following conclusions from her review of Arthrotec efficacy:

   A. Study 349 provides support for the efficacy of Arthrotec in the treatment of OA. Arthrotec 50 TID and Arthrotec 75 BID showed efficacy similar to diclofenac 75 BID and all three showed efficacy superior to placebo. This trial supports the use of Arthrotec only for patients using diclofenac 150mg daily.

   B. The use of Arthrotec for the treatment of RA is not supported by this application. Study 352 failed to demonstrate that diclofenac 75mg BID, Arthrotec 50 TID and Arthrotec 75 BID showed efficacy superior to placebo. The four remaining RA studies utilized flawed designs.

4. If bioequivalence is established between the Arthrotec formulation proposed for marketing and Voltaren, however, it will be unnecessary to re-prove efficacy with clinical studies, so that reservations described in the preceding paragraph will not be of consequence.

5. Concerning the firm's submitted draft labeling:

   A. Although the incidence of NSAID-induced gastric ulcers for Cytotec 200μg BID in Study 053 was significantly lower than placebo, it was numerically higher than the incidence for 200μg TID and QID(6.3% for BID, 3.2% for TID and 3.1% for QID). Dr. Botstein asked the firm if they intend to address this difference in the labeling. Searle replied that the labeling suggested using

Arthrotec two or three times per day as determined by the physician. Dr. Temple noted that misoprostol is indicated only for patients at high risk of complications from NSAID-induced peptic ulcers in which an ulcer or a bleed would be a serious matter and asked why it was reasonable to accept the lower effectiveness of the BID regimen except perhaps in people unable to tolerate the TID regimen. One possibility was to develop a 37.5 mg/200μg tablet to give a full range of doses. The firm replied that their physician surveys indicated that BID was used 70% of the time because of better tolerability and it was included in the labeling because they were trying to balance efficacy and tolerability. They agreed to consider labeling emphasizing the TID regimens (Arthrotec 50 or Arthrotec 75 TID giving 600 μg of misoprostol with 150 mg or 225 mg of diclofenac).

B. The Agency observed that, since Arthrotec is a fixed combination product, prescribers have less ability to individualize doses of both components then exists when the products are used separately. Dr. Fredd added that Arthrotec would be dosed based on the patients diclofenac needs, but that based on the data currently available, TID Arthrotec would not supply a misoprostol dose to prevent both DU and GU. Although it may be possible to handle this in the labeling by recommending a combination regimen involving Arthrotec supplemented with extra Cytotec tablets. Such a regimen may be confusing, difficult to adjust, and may obviate any possible compliance benefit.

C. Searle commented that they would like to limit and simplify the labeling and the Agency's considerations by proposing only gastric ulcer prevention at this time rather than both gastric and duodenal ulcer prevention.

D. The Agency commented that Arthrotec might be approved if reasonable labeling could be written and if the bioequivalence problem were solved.

E. The currently approved labeling for Cytotec recommends use in, "...patients at high risk of complications" from NSAID-induced peptic ulcers, the draft Arthrotec labeling recommends use in, "...patients at risk of developing NSAID-induced gastroduodenal ulcers". If the firm is arguing that Arthrotec is a "safer NSAID" and may be used for a broader patient population than Cytotec, they must provide support for this change.

F. The Agency recommended revising the draft labeling to be consistent with HFD-550s NSAID class labeling recommendations and with warnings currently in the Cytotec labeling. (Note: HFD-550s NSAID class labeling recommendations were faxed to the firm December 6, 1996.)

G. If bioequivalence is shown between Cytotec and Voltaren, information from

both labels, supplemented with Arthrotec data, may be included in the labeling. Deletions and additions from the Voltaren and Cytotec labels should be annotated.

The firm agreed to Dr. Botstein's request to submit revised labeling as well as a response to the November 22, 1996 biopharmaceutics information request letter as soon as possible.

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

Sincerely yours,

/S/

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
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cc:

Original NDA 20-607
HFD-180/Div. Files
HFD-180/CSO/B.Strongin
HFD-180/K.Robie-Suh
HFD-180/J.Choudary
HFD-180/G.Young
HFD-180/G.Chen
HFD-550/W.Chambers
HFD-550/J.Witter
HFD-550/L.Lobianco
HFD-720/M.Huque
HFD-720/M.Fan
HFD-850/L.Kaus

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Drafted by: BS/April 8, 1997/c:\wpfiles\n\20607704.0
final: BS/April 8, 1997

/S/ 4-8-97

GENERAL CORRESPONDENCE (MINUTES SENT)

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