CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 12, 1997

FROM: Brian Strongin, Regulatory Health Project Manager

SUBJECT: NDA 20-607, Arthrotec, Marked-Up Draft Labeling

TO: NDA 20-607

The attached marked-up draft labeling is based on the revised draft labeling submitted September 29, 1997 by the firm. All Agency comments arose from an internal labeling meeting December 4, 1997 and a meeting with Searle December 11, 1997. Attendees of both meetings are listed below. Since agreement with the firm was reached in the December 11, 1997 meeting, this labeling will be the basis for the "Approval on Draft" action to be taken.

December 4, 1997

Paula Botstein, M.D.	Director, ODE III
Bronwyn Collier	Special Assistant to the Director ODE III
Kathy Robie-Suh, M.D., Ph.D.	Medical Officer, HFD-180
Brian Strongin	Regulatory Health Project Manager, HFD-180
John Hyde, M.D., Ph.D.	Medical Team Leader, HFD-550
James Witter, M.D., Ph.D.	Medical Officer, HFD-180
Sharon Schmidt	Regulatory Health Project Manager, HFD-550

December 11, 1997

FDA

Paula Botstein, M.D.	Director, ODE III
Michael Weintraub, M.D.	Director, ODE V
Bronwyn Collier	Special Assistant to the Director ODE III
Kathy Robie-Suh, M.D., Ph.D.	Medical Officer, HFD-180
Brian Strongin	Regulatory Health Project Manager, HFD-180
James Witter, M.D., Ph.D.	Medical Officer, HFD-180
Sharon Schmidt	Regulatory Health Project Manager, HFD-550

Searle

R. Spivey, Pharm D., Ph.D.	V.P., Worldwide Regulatory Affairs
P. East	Associate Director, Regulatory Affairs
J. Lefkowith, M.D.	Director, Medical Affairs
P. Hamelin	V.P., U.S. Marketing
R. Bogomolny, Esq.	General Counsel
C. Wertjes, Esq.	Assistant General Counsel

cc:
NDA 20-607/Division File
HFD-180/Kathy Robie-Suh, M.D., Ph.D.
HFD-550/Sharon Schmidt

APPEARS THIS WAY
ON ORIGINAL

63 Page(s) Redacted

DRAFT LABELING

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

FEB - 1 1996

Application Number: 20-607

Name of Drug: Arthrotec (diclofenac sodium/misoprostol) Tablets

Sponsor: G.D. Searle & Company

Material Reviewed

Submission Date(s): December 22, 1995

Receipt Date(s): December 26, 1995

Background and Summary Description: This application was submitted for the acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in patients at risk of developing nonsteroidal anti-inflammatory drug (NSAID)-induced gastroduodenal ulcers.

G.D.Searle's Cytotec brand of misoprostol (NDA 19-268) has been approved for the prevention of NSAID-induced gastric ulcer in patients at high risk of complications from gastric ulcers since December 27, 1988.

An enteric coating was later developed for the market formulation.

The application contains seven pivotal studies; four in support of the osteoarthritis indication (Studies 349, 296, 289, and 321), and three in support of the rheumatoid arthritis indication (Studies 352, 289 and 292). Studies 349 and 352 use an Arthrotec formulation with the enteric coating; the other pivotal studies used the enteric coating. While

pivotal rheumatoid arthritis Study # 352 and osteoarthritis Study # 349 were conducted in the U.S., the other pivotal studies were multinational. All studies utilize a factorial design, and are randomized, parallel group, double blind, and multicenter, with the U.S. studies including a placebo arm. The studies were designed to compare the efficacy of Arthrotec to diclofenac and, in the U.S. studies, the efficacy of diclofenac was also compared to placebo. In addition, in four (RA Study #289 and OA Studies #349, 321, and 296) studies utilizing endoscopies, gastrointestinal mucosal damage associated with Arthrotec was compared to that associated with a diclofenac/placebo combination.

Review

1. Case report tabulations, as described on page 20 of the February 1987 edition of the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications", were not provided on a per-patient basis. Data was separated into multiple tables, i.e. "Patient Characteristics", "Efficacy Listings", "Adverse Events", and grouped within tables by investigator.

2. One case report form for pivotal Study #292 was in French (Volume 1.267, page 12-26,082). Although the case report form and the entries were both in French, an English translation of the blank case report form was provided in Appendix A.1 to the study report for Study #292 (Volume 1.83, page 8-15,741).

3. The table of all clinical studies, as described on page 13 of the July 1988 edition of the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application", deviated from the guideline in these respects:

    A. Lacked the starting date for the study
    B. Lacked the location of case report forms and case report tabulations

    Case report tabulations are included as an appendix to each study report with duplicates provided in Section 11 of the application. Case report forms are listed by study number

in the Table of Contents to the Application.

4. Investigator CVs for Study #298 ("Misoprostol/Diclofenac: Effect on the Signs and Symptoms of Osteoarthritis") could not be located.

Conclusions

A 45-day planning/filing meeting is scheduled for January 30, 1996. From an administrative standpoint, the application is acceptable for filing. After filing, the sponsor plans to submit a CANDA with the ability to resort and tabulate case report tabulations. The review team will discuss the need for case report tabulations on a per-patient basis at the team meeting. English translations of the case report forms, a revised table of clinical studies, and investigator CVs for #298 can be requested along with any other information identified by the respective reviewers.

/S/

Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

cc:
Original
HFD-180/Div. Files
HFD-180/BStrongin
HFD-180/SFredd

2/1/96 Concur
/S/

draft: BS/January 25, 1996/c:\wpfiles\n\20607601.0
r/d Initials: K.Johnson/January 30, 1996
B.Strongin/January 31, 1996
final: BS/January 31, 1996

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001. Expiration Date: December 31, 1995. See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
G.D. Searle & Co.	6-17-97
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
4901 Searle Parkway Skokie, IL 60077	(874) 982-8606
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
	20-607

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
diclofenac sodium/misoprostol	Arthrotec®

CODE NAME *(If any)*	CHEMICAL NAME
	2-[(2,6-dichlorophenyl)amino] benzeneacetic acid,mono-sodium salt/(±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS(S)
Tablet	Oral	50mg/200mcg 75mg/200mcg

PROPOSED INDICATIONS FOR USE

reatment of the signs and symptoms of osteoarthrits and rheumatoid arthritis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

AMENDED PATENT STATEMENT UNDER 21 USC 355(b)(1)

Drug Product (Drug) Patent

The previously identified U. S. patent 3,965,143 has now expired. There is no U. S. Patent now in existence directed to the drug misoprostol nor the drug diclofenac sodium contained in the fixed combination product which is the subject of the present application:

Drug Product (Formulation) Patents

The following U. S. Patents contain claims directed to formulations/dosage forms of the active agent misoprostol or the active agent misoprostol in combination with the active agent diclofenac sodium in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

Patent Number	Owner	Title	Expiration
4,301,146	G. D. Searle & Co.	Stabilization of 16-Oxygenated Prostanoic Acid Derivatives	July 29, 2000
5,601,843	G. D. Searle & Co.	Pharmaceutical Tablet Composition	February 11, 2014

The undersigned declares that the above patents cover formulations/dosage forms of the active agent misoprostol alone or in combination with the active agent diclofenac in the product which is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed U. S. Patents are assigned to G. D. Searle & Co., who is also the present NDA applicant.

Peter F. East

Peter F. East
Associate Director

APPEARS THIS WAY
ON ORIGINAL

PATENT STATEMENT UNDER 21 USC 355(b)(1)

Drug Product (Drug) Patent

The following U. S. Patent contains claims directed to the drug misoprostol which is contained in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

Patent Number	Owner	Title	Expiration
3,965,143	G. D. Searle & Co.	16-Oxygenated Prostanoic Acid Derivatives	Mar. 26, 1996

The undersigned declares that the above patent covers the active agent misoprostol in the product which is the subject of this application for which approval is being sought.

Drug Product (Formulation) Patents

The following U. S. Patent contains claims directed to formulations/dosage forms of the active agent misoprostol in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

Patent Number	Owner	Title	Expiration
4,301,146	G. D. Searle & Co.	Stabilization of 16-Oxygenated Prostanoic Acid Derivatives	July 29, 2000

The undersigned declares that the above patent covers formulations/dosage forms of the active agent misoprostol in the product which is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed U. S. Patents are assigned to G. D. Searle & Co., who is also the present NDA applicant.

CLAIMED PRODUCT EXCLUSIVITY Under 21 USC 355 D(iii)

The present applicant, G. D. Searle & Co. is claiming exclusivity under 21 CFR §314.108(b)(4) for the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application.

New Clinical Investigations:

The undersigned certifies that to the best of applicant's knowledge that each of the clinical investigations included in the present application meets the definition of "new clinical investigation" set forth in §314.108(a).

Essential to Approval:

The undersigned certifies that the applicant has thoroughly searched the scientific literature and, to the best of applicant's knowledge, there are no published studies or publically available reports of clinical investigation regarding the indications of acute and chronic treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis for a combination drug product containing the active ingredients misoprostol and diclofenac sodium in a fixed combination. The clinical studies contained in this application were determined to be essential to approval of the diclofenac sodium/misoprostol fixed combination tablet.

Conducted or Sponsored by:

The undersigned certifies that the applicant was the sponsor named in the Form FDA-1571 for an investigational new drug application under which the new clinical investigations which are essential to approval were conducted.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-607 SUPPL # _____

Trade Name Arthrotec Tablets
Generic Name diclofenac sodium/misoprostol
Applicant Name G.D. Searle & Company **HFD-** 180

Approval Date December 19, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity?

   YES /___/ NO /_X_/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-201 Voltaren (diclofenac sodium) Tablets

NDA # 19-268 Cytotec (misoprostol) Tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /_X_/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

   Despite the submission of clinical studies in support of efficacy and safety, approval could be based solely on a demonstration of bioequivalence between Arthrotec and the approved products, Cytotec Tablets and Voltaren Tablets.

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____
_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____
_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /__/
Investigation #2	YES /__/	NO /__/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____NO /___/ Explain_____

APPEARS THIS WAY
ON ORIGINAL

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ 12/15/97
Signature Date
Title: Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 12-15-97
Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-607 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Arthrotec Tablets Action: AP AE NA

Applicant G.D. Searle & Co. Therapeutic Class 4 S

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application See attached sheet. (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ /Regulatory Project Manager 9/8/97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-607
HF D-180 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

APPEARS THIS WAY
ON ORIGINAL

1 Page(s) Redacted

DRAFT LABELING

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # NDA 20-607 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Arthrotec Tablets Action: AP AE (NA)

Applicant G.D. Searle & Co. Therapeutic Class 4 S

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application See attached sheet. (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. See attached sheet. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ 3-12-97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # NDA 20-607
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

/S/ 3/12/97

Indication in this application:

For acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastroduodenal ulcers. Arthrotec contains misoprostol and enteric coated diclofenac sodium. The diclofenac sodium component provides the anti-arthritic efficacy and the misoprostol component provides gastroduodenal mucosal protection.

3. **PEDIATRIC STUDIES ARE NEEDED.**

Suggestions regarding pediatric studies will be forwarded when the application is approvable.

CERTIFICATION

Pursuant to section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant did not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b), in connection with this application.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 9, 1996

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Evaluation and Recommendation

TO: NDA 20-607

Searle submitted this application to market a fixed combination of an unapproved diclofenac product with the approved drug misoprostol.

The proposed labeling requests the following indication and dosage and administration:

"Indication
For acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastroduodenal ulcers. ARTHROTEC(R) contains misoprostol and enteric coated diclofenac sodium. The diclofenac sodium component provides the anti-arthritic efficacy and the misoprostol component provides gastroduodenal mucosal protection.

DOSAGE AND ADMINISTRATION

ARTHROTEC(R) is administered in tablets containing either a 50 mg diclofenac sodium enteric-coated core with a 200 mcg misoprostol mantle (ARTHROTEC(R) 50) or a 75 mg diclofenac sodium enteric-coated core with a 200 mcg misoprostol (ARTHROTEC(R)75).

Osteoarthritis: The usual dosage of ARTHROTEC(R)50 for the treatment of osteoarthritis is one tablet two or three times per day. This provides 100-150 mg/day of diclofenac sodium and 400-600 mcg/day of misoprostol. Dosage of ARTHROTEC(R)50 above three times per day have not been studied in patients with osteoarthritis.(16)

The usual dosage of ARTHROTEC(R)75 for the treatment of osteoarthritis is one tablet two times per day, which will provide 150 mg/day of diclofenac sodium and 400 mcg/day of misoprostol. Dosage of ARTHROTEC(R)75 above two times per day

have not been studied in patients with osteoarthritis.

Rheumatoid Arthritis: The usual dosage of ARTHROTEC(R)50 for the treatment of rheumatoid arthritis is one tablet two or three times per day. This provides 100-150 mg/day of diclofenac sodium and 400-600 mcg/day of misoprostol. Dosage of ARTHROTEC(R)50 above three times per day have not been studied in patients with rheumatoid arthritis.(24).

The usual dosage of ARTHROTEC(R)75 for the treatment of rheumatoid arthritis is one tablet two times per day, which provides 150 mg/day of diclofenac sodium and 400 mcg/day of misoprostol. Dosage of ARTHROTEC(R)75 above two times per day have not been studied in patients with rheumatoid arthritis.

Misoprostol alone, at doses of 400-800 mcg/day, is approved for the prevention of NSAID-induced gastroduodenal ulcers. (1) Single entity dosages of diclofenac sodium of 200 mg/day have not been studied in patients with osteoarthritis. Single entity dosages of diclofenac sodium above 150 mg/day have not been studied in patients with osteoarthritis. Single entity dosages of diclofenac sodium of 200 mg/day have been studied in patients with rheumatoid arthritis requiring more relief from pain and inflammation. Single entity dosages of diclofenac sodium above 225 mg/day are not recommended in patients with rheumatoid arthritis because of increased risk of adverse events.(2)

All recommended ARTHROTEC(R) regimens will deliver daily misoprostol doses of 400-600 mcg/day and daily diclofenac sodium doses of 100-150 mg/day, as shown in the following table.

	Regimen	Diclofenac Sodium (mg/day)	Misoprostol (mcg/day)
ARTHROTEC(R)50	BID	100	400
	TID	150	600
ARTHROTEC(R)75	BID	150	400

ARTHROTEC(R) should be taken with a meal. The tablets should be swallowed whole, and not chewed, crushed or dissolved.

Patients should be maintained on the lowest ARTHROTEC(R) dose

which provides satisfactory relief of the symptoms of arthritis." The approved indications and dosage for Ciba's diclofenac are:

"CATAFLAM Immediate-Release Tablets and VOLTAREN Delayed-Release Tablets, are indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. VOLTAREN-XR Extended Release Tablets are indicated for chronic therapy of osteoarthritis and rheumatoid arthritis. In addition, CATAFLAM Immediate-Release Tablets and VOLTAREN Delayed-Release Tablets are indicated for the treatment of ankylosing spondylitis. Only CATAFLAM is indicated for the management of pain and primary dysmenorrhea, when prompt pain relief is desired, because it is formulated to provide earlier plasma concentrations of diclofenac (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Clinical Studies).

DOSAGE AND ADMINISTRATION

Diclofenac may be administered as 50-mg CATAFLAM Immediate-Release Tablets, as 25-mg, 50-mg, and 75-mg VOLTAREN Delayed-Release Tablets, or as 100-mg VOLTAREN-XR Extended-Release Tablets. CATAFLAM Immediate-Release Tablets is the formulation indicated for management of acute pain and primary dysmenorrhea when prompt onset of pain relief is desired because of earlier absorption of diclofenac. For the same reason, VOLTAREN-XR is not indicated for the management of acute painful conditions and should be used as chronic therapy in patients with osteoarthritis and rheumatoid arthritis.

The dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The recommended dosage is 100 to 150 mg/day: CATAFLAM or VOLTAREN Delayed-Release 50 mg b.i.d. or t.i.d.; or VOLTAREN Delayed-Release 75 mg b.i.d. The recommended dosage for chronic therapy with VOLTAREN-XR is 100 mg q.d. Dosages of VOLTAREN-XR Extended-Release Tablets of 200 mg daily are not recommended for patients with osteoarthritis. Dosages above 200 mg/day have not been studied in patients with osteoarthritis.

Rheumatoid Arthritis: The recommended dosage is 100 to 200 mg/day: CATAFLAM or VOLTAREN Delayed-Release 50 mg t.i.d. or q.i.d.; or VOLTAREN Delayed-Release 75 mg b.i.d.. The recommended dosages for chronic therapy with VOLTAREN-XR is 100 mg q.d. In the rare patient where VOLTAREN-XR 100 mg/day is unsatisfactory, the dose may be increased to 100 mg b.i.d. if the

benefits outweigh the clinical risks. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

Ankylosing Spondylitis: The recommended dosage is 100 to 125 mg/day: VOLTAREN 25 mg q.i.d. with an extra 25-mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

Analgesia and Primary Dysmenorrhea: The recommended starting dose of CATAFLAM Immediate-Release Tablets is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of CATAFLAM, followed by 50-mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg."

The approved indication and dosages for Cytotec are:

"**INDICATIONS AND USAGE**
Cytotec (misoprostol) is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to prevent duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to prevent gastric ulcers in controlled studies of three months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

DOSAGE AND ADMINISTRATION
The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four time daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See Clinical Pharmacology: Clinical studies). Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.
Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See Clinical Pharmacology.)"

In acting on a supplemental application for duodenal ulcer prevention, we have recommended the 200 mcgm Q.I.D. dose which prevents both NSAID induced gastric and duodenal ulcer, with a T.I.D. dose as fall back for gastric ulcer prevention in patients unable to tolerate the Q.I.D. dose. We have also recommended elimination of the 100 mcgm Q.I.D. dose. As will be discussed in greater detail later, we found that T.I.D. was equivalent to Q.I.D. in gastric ulcer prevention but has not been shown in two studies to prevent duodenal ulcers. It was, however, better tolerated than Q.I.D. The B.I.D. dose appeared to be less

effective than either the Q.I.D. or T.I.D. dose for gastric ulcer prevention, had not been shown in two studies to prevent duodenal ulcers, and did not provide overall greater tolerance compared to T.I.D.

A fixed dose combination product must meet the requirements of 21 CFR 300.50 which states (in part):

> **(a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.**

In evaluating whether data are available to demonstrate that the conditions of each contributing a benefit to a significant portion of the patient population under the conditions of the proposed labeling, the medical, statistical and biopharmaceutics reviews should be consulted to provide the detailed information relevant to this report. The evaluation by the Acting Director of HFD-550 is appended to this report.

<u>The Diclofenac Component</u>

The diclofenac in the Arthrotec formulations is not the approved Ciba formulation. To establish the efficacy of that diclofenac, bioequivalence to Voltaren should be established. Adequate data have not been provided thus far.

While the sponsor performed clinical studies with related products in patients with Osteoarthritis (OA) and Rheumatoid Arthritis (RA), according to the sponsor these were meant to show that the efficacy of diclofenac was not diminished by the misoprostol, not as primary qualifying data for their diclofenac. Overall efficacy in RA was not demonstrated by these studies according to reviews from HFD-550.

Also, the US RA study (352) raises a question of whether T.I.D. misoprostol interferes with the efficacy of a 150 mg daily dose of diclofenac. In this study there were separate randomized arms of Arthrotec I and Arthrotec II. The statistical reviewer makes the following comment:

"Another unexplained finding is that Arthrotec II appeared to be more effective than Arthrotec I though both of them have a total dosage of 150 mg per day of diclofenac."

The data of concern are the following:

Table 10. Primary Efficacy Variables at Week 6 (ITT population)

Outcome	diclofenac BID N=107	Arthrotec I TID N=107	Arthrotec II BID N=111	Placebo n=55
Phy.'s Global				
Improved	28.0%	27.1%	28.2%	20.0%
Unchanged	71.0%	72.9%	70.9%	76.4%
Worsened	0.9%	0.0%	0.9%	3.6%
Baseline mean	3.5	3.6	3.4	3.5
LS mean change	-0.92	-0.92	-0.97	-0.66
Patient's Global				
Improved	27.1%	31.8%	30.9%	29.1%
Unchanged	72.0%	67.3%	68.2%	67.3%
Worsened	0.9%	0.9%	0.9%	3.6%
Baseline mean	3.6	3.6	3.6	3.6
LS mean change	-0.79	-0.80	-0.90	-0.63
Tender/Pain				
Baseline mean	28.2	31.5	29.4	29.9
LS mean Change	-10.16	-8.61	-13.34	-4.81
Swelling				
Baseline mean	20.1	23.0	22.6	20.8
LS mean change	-6.48	-5.86	-8.57	-3.53

Table 11. Primary Efficacy Variables at Week 12 (ITT population)

Outcome	diclofenac BID N=107	Arthrotec I TID N=107	Arthrotec II BID N=111	Placebo n=55
Phy.'s Global				
Improved	28.0%	25.2%	22.7%	14.5%
Unchanged	70.1%	74.8%	76.4%	81.8%
Worsened	1.9%	0.0%	0.9%	3.6%
Baseline mean	3.5	3.6	3.4	3.5
LS mean change	-0.90	-0.89	-0.81	-0.55
Patient's Global				
Improved	25.2%	28.0%	26.4%	20.0%
Unchanged	72.9%	69.2%	72.7%	76.4%
Worsened	1.9%	2.8%	0.9%	3.6%
Baseline mean	3.6	3.6	3.6	3.6
LS mean change	-0.71	-0.73	-0.75	-0.59
Tender/Pain				
Baseline mean	28.2	31.5	29.4	29.9
LS mean Change	-10.98	-8.82	-12.72	-4.09
Swelling				
Baseline mean	20.1	23.0	22.6	20.8
LS mean change	-6.22	-5.53	-8.03	-3.29

Table 20 - Table of P-Values of the Secondary Pairwise Comparisons from the Weeks 6 and 12 ITT Analysis of Study NN2-95-ST-352

Efficacy Variable	Arthrotec I t.i.d. vs. Placebo Wk 6	Arthrotec I t.i.d. vs. Placebo Wk 12	Arthrotec II b.i.d. vs. Placebo Wk 6	Arthrotec II b.i.d. vs. Placebo Wk 12	Arthrotec I t.i.d. vs. Arthrotec II b.i.d. Wk 6	Arthrotec I t.i.d. vs. Arthrotec II b.i.d. Wk 12
Physician's Global:						
LSM	p=0.072	p=0.025*	p=0.029*	p=0.089	p=0.651	p=0.501
Patient's Global:						
LSM	p=0.441	p=0.390	p=0.162	p=0.317	p=0.446	p=0.868
Tender Joints:						
LSM	p=0.183	p=0.101	p=0.003*	p=0.003*	p=0.043*	p=0.097
Swollen Joints:						
LSM	p=0.256	p=0.288	p=0.014*	p=0.024*	p=0.107	p=0.147

* Statistically significant p-values

The concern centers around the tender joint data at 6 and 12 weeks.

While there are a number of possible explanations for this observation, one is that patients taking two of the Arthrotec 75 tablets received B.I.D. misoprostol. Those taking three Arthrotec 50 received T.I.D. misoprostol. The higher misoprostol dose with the Arthrotec 50 tablets at the same total daily diclofenac dose might have interfered with the efficacy of diclofenac. The OA studies did not demonstrate a similar effect and the finding in the RA study may be spurious related to multiple comparisons.

Further consideration of this question by the sponsor might be warranted.

The Misoprostol Component

To prevent NSAID induced peptic ulcers, misoprostol can replace prostaglandin in the gastroduodenal mucosa and at certain doses provide an antisecretory effect. Dr. Michael Kimmey provided the following perspective at the 1996 American College of Gastroenterology postgraduate course as follows:

"IV. Prophylaxis of NSAID Induced Ulcers

Numerous studies have been done trying to find an agent that reduces the risk of NSAID induced ulcers. Most of these studies were conducted prior to the recognition of the

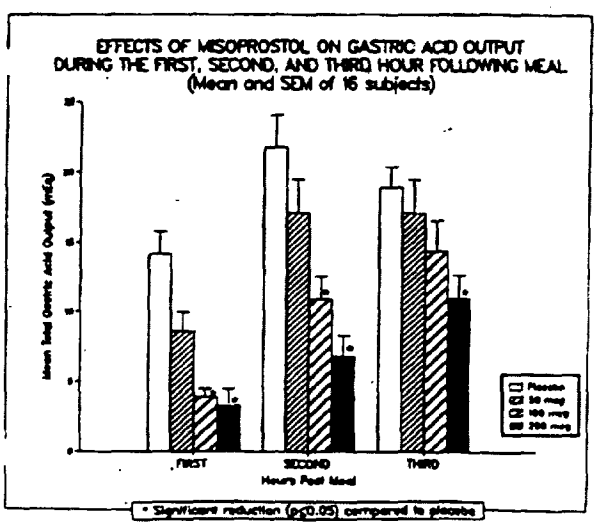
importance of *H. pylori*. Future prophylactic studies are needed that control for *H. pylori* status or evaluate the effect of prior *H. pylori* eradication on prophylaxis efficacy.

H2 receptor antagonists prevent duodenal, but not gastric ulcers due to NSAIDs. Higher doses of H2 receptor antagonists reduce the incidence of gastric ulceration, but do not appear to be as effective as misoprostol.[28] Sulcralfate does not prevent gastric ulcers secondary to NSAIDs and has not been adequately studied for duodenal ulcer prophylaxis.[29] Misoprostol prevents both gastric and duodenal ulcers and is more effective than ranitidine when studied in a head-to-head trial.[30] A similar efficacy may be achieved using a misoprostol dose of 200µ gm three times daily rather than the conventional dose of four times daily, but 200µ gm twice daily is less effective.[31] Misoprostol has also been shown in a study of nearly 9,000 rheumatoid arthritic patients to reduce ulcer complications by 40%[6]. Similar to other studies, 20% of patients in this trial dropped out in the first month because of diarrhea and other side effects.

Use of proton pump inhibitors for NSAID ulcer prophylaxis is under active study. Three recent abstracts have shown a benefit of using 20 mg of omeprazole over either ranitidine or placebo in preventing ulcers and dyspepsia in patients taking NSAIDs.[32-34] The benefit appears to be present for gastric as well duodenal ulcers.[33,34] U.S. trials using lansoprazole for preventing NSAID ulcers are in progress."

The antisecretory effects of various single misoprostol doses is depicted in the following display from the original Cytotec NDA.

Figure 4



While all doses had some antisecretory effect, 200 mcgm had the largest and most prolonged effect, though only out to three hours. To maintain an antisecretory effect frequent dosing over a 24 hour period may be needed.

For duodenal ulcer treatment it was clear that more than a transient antisecretory effect was needed for healing. One study gave these healing results.

Table 21

Therapeutic Outcome
Intent-to-Treat Cohort
(All Subjects)
Week 4

Number (%) of Subjects

A. Complete Table

(Placebo vs. 50 mcg vs. 200 mcg)

Treatment	Success	Failure†	Totals
Placebo	51 (51.0%)	49 (49.0%)	100 (100.0%)
50 mcg	43 (42.6%)	58 (57.4%)	101 (100.0%)
200 mcg	82 (76.6%)	25 (23.4%)	107 (100.0%)
Totals	176 (57.1%)	132 (42.9%)	308 (100.0%)

Pearson χ^2 [2 df] = 26.895 p = .000001

B. Partitioned Tables

(Placebo vs. 50 mcg)

Treatment	Success	Failure†	Totals
Placebo	51 (51.0%)	49 (49.0%)	100 (100.0%)
50 mcg	43 (42.6%)	58 (57.4%)	101 (100.0%)
Totals	94 (46.8%)	107 (53.2%)	201 (100.0%)

Pearson χ^2 [1 df] = 1.457 p = .227

(Placebo + 50 mcg vs. 200 mcg)

Treatment	Success	Failure†	Totals
Placebo + 50 mcg	94 (46.8%)	107 (53.2%)	201 (100.0%)
200 mcg	82 (76.6%)	25 (23.4%)	107 (100.0%)
Totals	176 (57.1%)	132 (42.9%)	308 (100.0%)

Pearson χ^2 [1 df] = 25.439 p = .0000005

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In this study the drugs were given Q.I.D. and this result is representative of the clinical data where it was concluded that for duodenal ulcer healing a prolonged antisecretory effect of the drug was needed.

In NSAID induced duodenal ulcer prevention, two Cytotec studies clearly establish the benefit of the 200 mcgm Q.I.D. dose regimen (studies 053 and 041). In no case was that regimen studied with a null result. On the other hand the 200 mcgm B.I.D. dose regimen was significantly effective in one study (053) and null in three others (551, 136, and 349). The T.I.D. dose was also effective in one Cytotec study (053), but null in two others (296 and 349), both Arthrotec studies.

An overview of efficacy of various dose regimens in duodenal and gastric ulcer prevention is provided by the following chart, slightly adapted from Dr. Robie-Suh's review.

Dosing Regimen		Gastric Ulcer	Duodenal Ulcer
200mcg	Q.I.D.	Study 053 Study 002 Study 003	Study 053 Study 041
200mcg	T.I.D.	Study 053[a] Study 320 Study 349	Study 053
200mcg	B.I.D.	Study 053* Study 349	Study 053
100mcg Q.I.D.		Study 002[b]	----

[a] misoprostol 200mcg TID therapeutically equivalent to misoprostol 200mcg QID.
[b] misoprostol 200mcg QID was superior to 100 mcg QID.
*BID not equilvalent to TID.

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 GU prophylaxis, not yet established for DU prophylaxis, and well tolerated. The B.I.D. does not demonstrate equivalent efficacy for GU prophylaxis to Q.I.D. and T.I.D., and is not yet established for DU prophylaxis.

An additional study of the T.I.D. regimen for DU prophylaxis seems needed if one seeks replication of the 053 study (given that two other studies were null). I would recommend that given the high risk nature of the patients and the question of frequency of dosing and maintenance of antisecretory effect needed for duodenal ulcer healing and several null Arthrotec studies of the T.I.D. regimen for DU prophylaxis, a replicative study should be provided.

To establish an adequate database to determine the efficacy of misoprostol in the Arthrotec fixed dose combination we have agreed with Searle that data from the Arthrotec and Cytotec NDAs should be considered. However, bioequivalence of the Arthrotec market images to marketed Cytotec must be provided to do that.

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. 200 mcgm of misoprostol are present in each tablet as well. With a dose regimen of 100-200 mg (or 225) of diclofenac possible for the treatment of OA and RA as per the Voltaren labeling (with individualization of dosing emphasized in the labeling), would the proposed formulations of Arthrotec on their own supply NSAID induced peptic ulcer protection for a significant portion of the patient population i.e. those with OA and RA at high risk of serious complications of NSAID induced ulcers. Since the OA population would received two or three Arthrotec tablets, they would not receive misoprostol in the 200 mcgm Q.I.D. dose. In the future were we to conclude that the T.I.D. dose was as effective for GU and DU as the Q.I.D. dose, only those OA patients taking 3 Arthrotec 50 tablets daily would receive the 200 mcgm T.I.D. dose.

For RA patients, currently only those who would take Arthrotec 50 four times a day (giving 200 mg of diclofenac) would receive the currently recommended 200 mcgm Q.I.D. dose.

Neither tolerability nor individualization of diclofenac dosing considerations add to the utility of the Arthrotec formulations. Lowering the diclofenac dose for RA or OA would provide less

gastric or duodenal ulcer protection then might be possible and tolerated with the single diclofenac and misoprostol drug products. A compliance benefit, however, could be provided by Arthrotec.

Certain labeling proposals have been suggested to deal with some of the dosing problems enumerated.

1. Restrict the misoprostol claim to GU prophylaxis alone. This would make T.I.D. the dose regimen of choice.

   Since we now know that Q.I.D. is also effective for DU prophylaxis and the patient population to be treated is high risk, such labeling can be considered inadequate re safety. Establishing the T.I.D. dose as effective in preventing duodenal ulcers is preferable to this suggestion.

2. Add additional Cytotec tablets as needed to give the appropriate misoprostol dose regimen. This may well be necessary, but with the currently approved or approvable dose regimens of the components, a very complex and changing series of instructions would be needed. For example, the OA patient needing 150 mg of diclofenac would either take 3 Arthrotec 50s and 1 Cytotec tablet or 2 Arthrotec 75s with 2 Cytotec tablets. If there was intolerance to the Cytotec Q.I.D. dose, either 3 Arthrotec 50s could be taken or 2 Arthrotec 75s with 1 Cytotec. When the patients dose of diclofenac changed, other instructions would be needed. This is more complex than dealing with the two drugs individually, and could lead to misuse of the Arthrotec formulations.

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 must be concerned that these fixed dose formulations as used may not provide an adequate Cytotec dose.

We have been notified that the sponsor intends to amend the application before the December 26, 1996 action date. I would recommend a three month extension to further review the new proposals and analyses. A joint Arthritis-GI advisory committees might consider the adequacy of the data and proposed labeling so

that we could have some open public discussion of the issues.

Since the Acting Director, ODE-III, has requested an evaluation of the situation at this time for action by December 26, 1996, this memorandum is offered together with the recommendation for a not approvable letter based on the data available if action needs to be taken at this time.

The following deficiencies should be transmitted to the sponsor if we issue an action letter at this time.

1. Data should be submitted from studies which directly compare the proposed market image of Arthrotec to marketed Voltaren and Cytotec to demonstrate that diclofenac in the Arthrotec market image and misoprostol in the Arthrotec market images are bioequivalent to Voltaren and Cytotec.

2. A clinical study of Arthrotec formulations should be provided to confirm the results study 053 for the T.I.D. misoprostol dose regimen in preventing diclofenac induced duodenal ulcer.

3. The difference in response for Arthrotec 50 and Arthrotec 75 in study 352 should be considered. An additional study to determine whether there is a diminution of diclofenac's efficacy when misoprostol is coadministered at doses of 200 mcgm T.I.D. or higher might also be considered.

4. The unequal numbers of patients allocated to the different treatment groups in study 349 should be considered with an explanation of how the randomization procedure resulted in the different sizes of the groups.

5. The labeling should be revised to include all warnings, precautions etc. present in the approved Voltaren and Cytotec labels.

Other comments and questions as contained in the biopharmaceutics and manufacturing controls letters of November 22, 1996 and December 5, 1996 respectively should be responded to, but

resolution of these issues are not critical to approval.

/S/

Stephen Fredd, M.D.

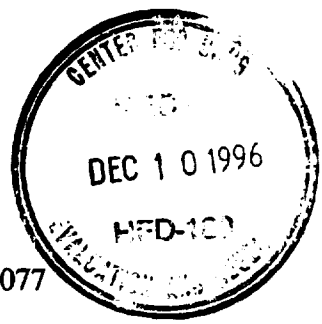
cc:
NDA 20-607
HFD-180
HFD-002/Dr. Lumpkin
HFD-100/Dr. Temple
HFD-103/Dr. Botstein
HFD-105/Dr. Weintraub
HFD-540/Dr. Chambers
HFD-550/Dr. Hyde
HFD-560/Dr. Neuner
HFD-180/Dr. Robie-Suh
HFD-550/Dr. Leung
HFD-181/CSO/Mr. Strongin
HFD-180/SFredd: 12/9/96
f/t by deg: 12/9/96/12/13/96 wpc:\wpfiles\fredd\m\nda20607.1sf

APPEARS THIS WAY
ON ORIGINAL

Division Director's Consultative Memorandum of NDA 20-607

NDA 20-607

Date: 12/9/96



Drug name: Arthrotec
Generic name: diclofenac sodium/misoprostol

Applicant: G.D. Searle & Co.
4901 Searle Parkway, Skokie, IL 60077

Related Reviews: Medical Officer Consult Review (Neuner) dated 12/2/96
Statistical Review and Evaluation (Leung) dated 9/24/96

Background:

The proposed product is a fixed combination of diclofenac sodium 50 mg or 75 mg combined with misoprostol 200 μg. Diclofenac is a nonsteroidal anti-inflammatory drug product approved for acute and chronic symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The recommended dose range for the treatment of osteoarthritis is 100 to 150 mg per day in divided doses. The recommended dose range for the treatment of rheumatoid arthritis is 150 to 200 mg per day in divided doses. Misoprostol is a prostaglandin E_1 analogue approved for the prevention of NSAID-induced gastric ulcers in patients at high risk for complications from gastric ulcers.

The Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550) has been asked to review and comment on the studies submitted to support the use of Arthrotec in the treatment of osteoarthritis and rheumatoid arthritis.

This memorandum is limited to comments concerning the evaluation and labeling of claims involving osteoarthritis and rheumatoid arthritis. Dr. Neuner's consultative review contains the specific details of the studies identified in this memorandum. A full evaluation of safety which would include the endoscopy results has not been performed by HFD-550.

Osteoarthritis:

The use of Arthrotec in the treatment of osteoarthritis 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 bid was equivalent to diclofenac 50mg/misoprostol 200μg tid and diclofenac 75mg/misoprostol 200μg bid. Questions remain concerning the adequacy of the randomization in this trial since there was an unequal distribution of patients between groups. At best, the evidence would support the use of arthrotec only for those osteoarthritis patients needing 150 mg of diclofenac per day. The submitted studies are not sufficient to support comparative claims between Arthrotec and either piroxicam or naproxen.

Rheumatoid arthritis:

The use of Arthrotec in the treatment of rheumatoid arthritis is not supported in the submitted application. The principal efficacy study (NN2-95-ST-352) failed to demonstrate that diclofenac 75 mg bid, diclofenac 50mg/misoprostol 200μg tid, or diclofenac 75mg/misoprostol 200μg bid was clinically superior to placebo. There are several potential explanations for the failure to demonstrate efficacy including the formulation of diclofenac, the selected target population, the variability identified between investigators and the dose chosen for this study (low end of the approved dose range).

Bioequivalence studies:

The use of Arthrotec in the treatment of osteoarthritis and rheumatoid arthritis is not supported by bioequivalence studies because studies have not been submitted to establish the bioequivalence between the proposed market formulation and the reference product for diclofenac (Voltaren). It is not immediately obvious based on the manufacturing information that the products are bioequivalent. Consideration could be given to permitting the full approved range of diclofenac in Arthrotec, if **after the submission and review,** studies demonstrate bioequivalence between Arthrotec and the diclofenac reference drug product.

Labeling:

The applicant's proposed labeling is not supported by the submitted studies, is not consistent with approved dose range of diclofenac for each of the proposed indications and is not consistent with the class labeling recommendations for NSAIDs. In addition, information supporting the change in the target population (i.e., no longer limited to patients at high risk for complications from gastric ulcers) has not been submitted.

Recommendations:

NDA 20-607, as submitted is not recommended for approval because there is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. The applicant should be encouraged to:

1. Perform and submit studies comparing the bioavailability of the approved diclofenac reference product (Voltaren) with Arthrotec.

2. Revise the proposed labeling to be consistent with diclofenac's approved dose ranges for each of the specific indications.

3. Revised the proposed labeling to be consistent with the NSAID class labeling recommendations.

4. Revised the proposed labeling to be consistent with the limited population of patients at high risk for complications due to gastric ulcers or provide an adequate justification for altered benefit to risk ratio for the new target population.

5. Provide an explanation for imbalance between the number of patients in each group of study NN2-94-02-349.

While there may be sufficient evidence to support the use of Arthrotec in the treatment of osteoarthritis at diclofenac 150 mg equivalent doses per day, the limitation to only this single supported dose would promote an unexplained inconsistency in the recommended dosing between this product and the diclofenac reference product. In addition, major labeling revisions as identified above would still be required.

/S/

APPEARS THIS WAY
ON ORIGINAL

Wiley A. Chambers, M.D.
Acting Division Director, HFD-550

cc: NDA 20-607
HFD-103
HFD-105
HFD-180
HFD-550
HFD-560/Neuner
HFD-550/Hyde

APPEARS THIS WAY
ON ORIGINAL

DEPUTY DIRECTOR CONSULT REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS DIVISION -- HFD-550

NDA #:	**20-607**
SUBMISSION DATE:	June 18, 1997.
TYPE:	Proposed Labeling
REVIEW DATE:	September 2, 1997.
REVIEWER:	John Hyde, Ph.D., M.D.
NAME:	**Arthrotec** (diclofenac/misoprostol, 50 mg/200 mg and 75 mg/200 mg)
SPONSOR:	G. D. Searle & Co.
PHARMACOLOGIC CATEGORY:	NSAID/PG inhibitor.
PROPOSED INDICATIONS:	OA and RA.
DOSAGE FORM & ROUTE:	Tablet, oral.
NDA DRUG CLASSIFICATION:	4S
RELATED REVIEWS:	HFD-550 MO Consult Review of 8/27
CSO:	LoBianco (HFD-550) Strongin (HFD-180)
MATERIALS REVIEWED:	Draft labeling dated 6/17/97.

This review is a supplement to the MO Consult Review dated 8/27/97 by Dr. Witter. My remarks are divided in to major comments--changes I would definitely make; secondary comments--those I would make but are somewhat dependent on divisional labeling philosophy; and editorial comments.

Major Comments

GENERAL

The most rational use of this product would be for patients who have been individualized on diclofenac and misoprostol separately, and for whom the dosing happens to match what is available with an Arthrotec formulation. However, it would be too heavy-handed to so limit the indication. Still, consideration of that strategy should be described prominently in DOSING AND ADMINISTRATION.

Page 7, CLINICAL STUDIES, Osteoarthritis

I reaffirm Dr. Witter's comment that the second sentence of the first paragraph of this section need to be deleted, because 200 mg is not a recommended dose for OA.

Page 11, INDICATIONS AND USAGE

There is too much deviation from the wording in the Cytotec labeling. It would be a significant broadening of the indication from that of Cytotec to cite simply *increased* risk. I defer to HFD-180 on the inclusion of duodenal ulcers.

The indicated population should be those "... at *high* risk of complications from NSAID-induced gastric or duodenal ulcers, as well as patients at *high* risk of developing NSAID-induced gastric or duodenal ulcers, but for whom NSAID therapy is still required." (Italics only for emphasis in this review.) I added that last clause because, unlike misoprostol alone, which is indicated to reduce the risk of a high risk situation, this labeling is actually *indicating* an NSAID product in a high risk population. The message should NOT be to give this when you might otherwise turn away from NSAID's because of the risk (the message the applicant might be wishing to give), rather the message should be to consider giving this if you feel you need to give NSAID's despite some significant risk.

I second Dr. Witter's remarks in discouraging the listing of risk factors in the indication; it tends to attract attention to the risk for ulcers, to the detriment of attention to the risk for *complications* of ulcers. I would substitute a referral to the GI WARNING section.

The last sentence in the Cytotec labeling was valuable, and should be carried over: "[Misoprostol] had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use."

Pages 11-20, WARNINGS and PRECAUTIONS

The sponsor should restore the class warnings and precautions (excepting the diclofenac-specific ones) to match the text in the NSAID template. The applicant's modifications do not strengthen the sections. At best they give product-specific information that does little to make the sections more informative; at worst they are attempts at self-promoting disclaimers that add bulk to a long labeling. If HFD-550 is to be able to maintain the class labeling, such customization should be discouraged unless it materially enhances the warnings or precautions.

In particular:

GI WARNING, p.12: The last paragraph should be stricken. In the paragraph above, the reference to H2-antagonists and antacids has not been accepted by the division. However, the risk factor of H. pylori was an overlooked in the template and should be added here.

Anaphylactoid Reactions, p. 14: Strike last sentence.

Renal Effects, pp. 15-16: This is in wrong order among precautions. The first paragraph from template was not included. The third paragraph on p. 16 should be omitted.

Anticoagulants, p. 19: Should read per NSAID template for warfarin.

Page 28, DOSAGE AND ADMINISTRATION
Same comments as above concerning indications and in the general comment.

Secondary Comments

Page 7, Analgesic Properties
I recommend striking the entire section. The product does not have an analgesic indication. We were unaware of these analgesic studies and have not reviewed them. It is not clear how relevant this is to approved indications, anyway. In fact, study 95-06-349 in OA found Arthrotec II BID (75/200) tending to be more effective than Arthrotec I TID, suggesting (but certainly not establishing) that misoprostol may interfere slightly with the diclofenac efficacy. This section doesn't help the prescriber much, appears to encourage unapproved uses, has promotional qualities that may be abused in advertising, and adds to labeling bloat.

Pages 7-9, CLINICAL STUDIES
Statements that misoprostol had no influence on efficacy should be removed. The studies were not capable of showing equivalence, and at least one study had a week suggestion of decreasing efficacy with higher misoprostol dose.

In general this reviewer's preference would be to shorten the OA and RA sections significantly. At lot of space is used just to say that the product worked for the indications, but I recognize divisional styles differ. The comparisons may be informative, but the statements should be weak. E.g., the comparisons to piroxicam and naproxen (page 8, last paragraph of OA section) should be "similarly effective" rather than "as effective."

Pages 25-27, ADVERSE REACTIONS
The four separate sections (occasionally, rarely, misoprostol but not Arthrotec, and diclofenac but not Arthrotec) should be merged. It makes the section very long, and I do not see how the separation helps in practice.

At any rate, the lead-ins to the last two sections seem to boarder on disclaimer: were reported for X, BUT not seen in Arthrotec trials (?!, meaning you shouldn't expect to see it with Arthrotec?). If the separate sections are retained, they should at least read something like "were not seen in Arthrotec trials, but have been reported with X and so should be expected with Arthrotec as well."

Editorial Comments

Page 23, ADVERSE REACTIONS, Gastrointestinal
One of this reviewer's pet peeves is empty precision such as that demonstrated in the first paragraph of this section. Whole percentages would do nicely.

Page 24, *Skin and Appendages*
"Pruritus" is misspelled.

Other Issues

This division had raised the concern of the suspicious imbalance in the randomization of one of the studies. Although the applicant's response was not fully comforting, there are insufficient grounds to reject the study, and we will consider the matter closed.

/S/ 9-2-97
John E. Hyde, Ph.D., M.D.

Orig NDA # 20-607
HFD-180/Div File
HFD-180/CSO/Strongin
HFD-550/Div File
HFD-550/CSO/LoBianco
HFD-550/MO/Hyde
HFD-550/MO/Witter