

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 / / 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 / /

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 _____

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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 /
Signature _____ Date 2/15/97
Title: Project Manager

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

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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

HF^D-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.
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/ SOImstead (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)

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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

HF D-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.
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/
Signature of Preparer and Title

3-12-97
Date

cc: Orig NDA/PLA/PMA # NDA 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)

/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.

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Arthrotec
New Drug Application
Debarment Certification

Page 1 of 1
RA-ART-9
20 Dec 1995

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.

**APPEARS THIS WAY
ON ORIGINAL**

4/10/97

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.

	<u>Regimen</u>	<u>Diclofenac Sodium</u> <u>(mg/day)</u>	<u>Misoprostol</u> <u>(mcg/day)</u>
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.

DOSEAGE AND ADMINISTRATION

The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four times 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.

The Diclofenac Component

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

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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		Arthrotec II b.i.d. vs. Placebo		Arthrotec I t.i.d. vs. Arthrotec II b.i.d.	
	Wk 6	Wk 12	Wk 6	Wk 12	Wk 6	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

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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

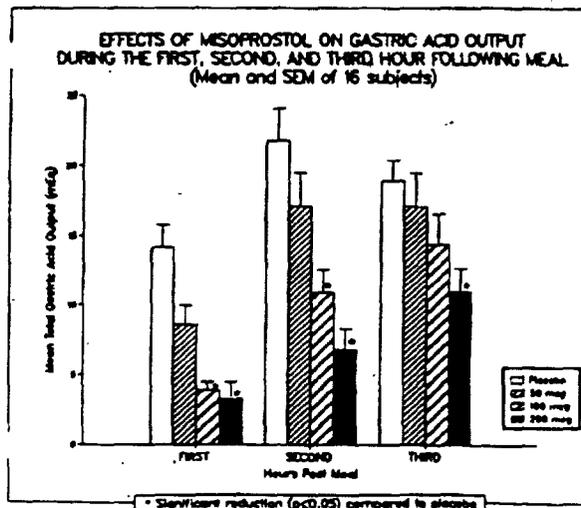
importance of *H. pylori*. Future prophylactic studies are needed that control for *H. pylori* status or evaluate the effect of prior *H. pylori* eradication on prophylaxis efficacy.

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



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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

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Number (%) of Subjects

A. Complete Table

(Placebo vs. 50 mcg vs. 200 mcg)

Treatment	Success	Failure?	Totals
Placebo	51 (51.00)	49 (49.00)	100 (100.00)
50 mcg	43 (42.60)	58 (57.40)	101 (100.00)
200 mcg	82 (76.60)	25 (23.40)	107 (100.00)
Totals	176 (57.10)	132 (42.90)	308 (100.00)

Pearson χ^2 [2 df] = 26.893 p = .000001

B. Partitioned Tables

(Placebo vs. 50 mcg)

Treatment	Success	Failure?	Totals
Placebo	51 (51.00)	49 (49.00)	100 (100.00)
50 mcg	43 (42.60)	58 (57.40)	101 (100.00)
Totals	94 (46.80)	107 (53.20)	201 (100.00)

Pearson χ^2 [1 df] = 1.457 p = .227

(Placebo + 50 mcg vs. 200 mcg)

Treatment	Success	Failure?	Totals
Placebo + 50 mcg	94 (46.80)	107 (53.20)	201 (100.00)
200 mcg	82 (76.60)	25 (23.40)	107 (100.00)
Totals	176 (57.10)	132 (42.90)	308 (100.00)

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 equivalent 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

NDA 20-607

Page 14

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

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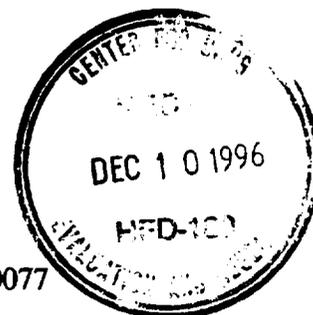
Division Director's Consultative Memorandum of NDA 20-607

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 μ g. 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 E₁ 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.

NDA 20-607 : Arthrotec

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 200 μ g tid and diclofenac 75mg/misoprostol 200 μ g 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 200 μ g tid, or diclofenac 75mg/misoprostol 200 μ g 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/

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

**APPEARS THIS WAY
ON ORIGINAL**

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

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-607 : Arthrotec

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 weak suggestion of decreasing efficacy with higher misoprostol dose.

In general this reviewer's preference would be to shorten the OA and RA sections significantly. A 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 border 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.

**APPEARS THIS WAY
ON ORIGINAL**

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

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

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

CORRESPONDENCE

NDA 20-607

MAR 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 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 μ g T.I.D. and diclofenac 75 mg/misoprostol 200 μ g 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 μ g Q.I.D. dose regimen (studies 053 and 041). In no case was that regimen studied without effectiveness. On the other hand, the 200 μ g 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 to the marketed Voltaren 50 mg tablet 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 200 μ g T.I.D. dose, but not those patients requiring the 100 mg diclofenac daily. No patient with OA would receive the 200 μ g 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 μ g 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 μ g 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.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-607
Page 6

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

Sincerely yours,

/S/

3/26/97

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

**APPEARS THIS WAY
ON ORIGINAL**

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)

IS/ 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/misoprotol)**

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,

A handwritten signature in black ink that reads "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\m\20607605.0

YSJ | 5-3-96

ADVICE

YSJ 5/6/96

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ON ORIGINAL

Strongin

NDA 20-607

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

APR 15 1986

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.d

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ON ORIGINAL

BS/ 4/12/96

BS/ 4/12/96

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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

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

APPEARS THIS WAY

NDA 20-607

Page 2

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cc:

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

/ST/ may 22, 1997

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

final: LT/May 22, 1997

GENERAL CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

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/ 5-5-97

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

enclosed documents:

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

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ON ORIGINAL

NDA 20-607
Page 2

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

BS/5-5-97

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

GENERAL CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

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

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NDA 20-607

Page 2

cc:

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

APPEARS THIS WAY
ON ORIGINAL

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

/S/ 4/17/97

/S/ 4/18/97

GENERAL CORRESPONDENCE

APPEARS THIS WAY

8.1

NDA 20-607

DEC - 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.
Robert Temple, M.D.

Deputy Center Director for Review Management
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 200 μ g 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 μ g 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 200 μ g QID for the prevention of NSAID-induced duodenal ulcers with an alternative dosage of 200 μ g 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 400 μ g - 600 μ g/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-arthritis 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 μ g BID of misoprostol) and TID (200 μ g 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 200 μ g 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 200 μ g BID in Study 053 was significantly lower than placebo, it was numerically higher than the incidence for 200 μ g 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/200 μ g 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 μ g 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 than 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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NDA 20-607

Page 9

cc:

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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)

APPEARS THIS WAY
ON ORIGINAL