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from sponsor's table, NDA Vol. 1.101, pp. 8-24513 through 8-24521

B. **Objectives:** The objectives of this study were (1) to identify among patients with rheumatoid arthritis or osteoarthritis those patients having clinically significant gastric or duodenal lesions and to determine the incidence of these among NSAID users, (2) to assess [in the treatment phase] the safety and efficacy of misoprostol 800mcg daily, given open label, in treating these lesions, and (3) for the double-blind phase of the study to assess the effect of misoprostol 200mcg coadministered with diclofenac 50mg given two to three times daily for up to one year [German centers 24 weeks] in preventing clinically significant upper gastrointestinal lesions associated with diclofenac, to assess the effect on total upper gastrointestinal score and symptoms, to assess the antiarthritic efficacy of the coadministration, and to assess the safety of diclofenac and misoprostol when given together.

C. **Study Description:** Male or female patients aged 18 or older having rheumatoid arthritis or osteoarthritis and taking NSAIDs for more than 6 months (or who required chronic NSAID therapy but were not able to tolerate continuous NSAID due to gastrointestinal side effects) underwent upper endoscopy. Those patients found to have upper gastrointestinal hemorrhage, gastric or duodenal ulceration, or more than 10 erosions in the corpus, antrum or duodenum were enrolled in an open-label treatment phase during which patients received misoprostol 200mcg q.i.d. for 6 weeks. During this phase for some patients NSAIDs were stopped; other patients continued NSAID treatment. At the end of this phase patients having no lesions or minimal lesions (<4 erosions, <10 petechiae and no evidence of gastrointestinal hemorrhage or ulceration) were to proceed to the prophylaxis phase of the study. For this double-blind phase of study patients were randomized to diclofenac 50mg + placebo two or three times daily or to diclofenac 50mg + misoprostol 200mcg two or three times daily. Dosage regimen (b.i.d. or t.i.d.) was at the discretion of the investigator for optimal control of the arthritis and was allowed to be increased or decreased during the study as needed. Treatment assignment was stratified by type of arthritis (rheumatoid arthritis or osteoarthritis).

The study was amended to provide that in German centers misoprostol was supplied by the sponsor but diclofenac was given to patients by investigators as a prescription. Patients assigned to a t.i.d. regimen returned to clinic every 3 weeks for prescription refill and every 6 weeks for followup. Those assigned to b.i.d regimen returned every 6 weeks for followup. The study

also was amended to allow in England inclusion of subjects who took NSAIDs for 4 of the 5 weeks prior to screening and were found to have significant gastrointestinal lesions. In England, at follow-up endoscopy, gastric biopsy was allowed.

At study initiation a mucosal grading scale which entailed grading bleeding, erosions, and erythema separately was stipulated; however, this scale was revised and the revised scale is used in the study report. The Revised Mucosal Grading Scale used in this study differs somewhat from the scale used in Study 349. The scale is as follows:

Revised Mucosal Grading Scale

Score	Description
0	Normal
1	1-10 petechiae
2	>10 petechiae or coalescent intramucosal blood
3	1-3 erosions**
4	4-10 erosions
5*	>10 erosions
6*	oozing or intraluminal blood
7*	ulceration+ or visible vessel

* clinically significant lesion
** An erosion is defined as a break in the mucosa by without a fibrous base.
+ An ulcer is defined as a break in the mucosa with a fibrous base.

NDA Vol. 1.101, p. 8-24173

D. **Results:**

1. **Enrollment and Baseline Characteristics of Patients**: The total number of patients screened and the number treated in the treatment phase are not given in this study report. For the double-blind prophylaxis phase, a total of 384 patients were randomized.

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Study 269: Enrollment of Patients by Center

Investigator No.	Investigator	Diclofenac 50mg +Placebo BID-TID	Diclofenac 50mg +Misoprostol 200mcg BID-TID	Total
AR0001	Onetti	5	5	10
AR0002	Scheines	2	2	4
BE0001	D'Hondt	2	0	2
BE0002	Van Kerckhove	8	8	16
BE0003	Devis	1	1	2
BE0004	Rimbaut	2	0	2
BE0005	Raeman	2	3	5
CA0001	Blondin	2	2	4
CA0002	Jovaisas	0	3	3
CA0004	Thompson	5	4	9
CA0007	Dunne	2	1	3
CO0001	Chalem	6	6	12
CO0002	Pena	6	8	14
FI0001	Yli-Kettula	1	0	1
FI0002	Jaaskelainen	1	3	4
FI0003	Elomaa	0	2	2
GE0002	Bohl	10	10	20
GE0004	Grote	5	5	10
GE0006	Worner	4	4	8
GE0009	Biermann	0	4	4
GR0001	Arvanitakis	10	10	20
GR0003	Nakos	2	4	6
GR0004	Skandalis	1	1	2
GR0005	Voudouris	2	1	3
NE0001	Bijlsma	3	0	3
PO0001	Teixeira	4	4	8
SA0001	Marks	10	9	19
SA0002	Simjee	9	5	14
SA0003	Buchel	5	4	9
SA0004	Bam	0	2	2
SA0005	Klemp	7	6	13
SW0001	Liedberg	2	3	5
SW0002	Strom	6	5	11
SW0003	Wikander	1	2	3
UK0001	Gumpel	6	5	11
UK0002	Hollingworth	2	0	2
UK0005	Darlington	1	0	1
UK0007	Price	0	3	3
US0001	Cheatum*	15	14	29
US0002	Miller	0	3	3
US0003	Roufail	3	3	6
US0004	Wilson	1	0	1
US0005	Jones	0	2	2
US0006	Roth*	6	6	12
US0007 US0008	Agrawal*	9	9	18
US0009	Lies	3	3	6
US0010	Nickeson	5	4	9
US0011	Toth	2	1	3
US0012	Ettlinger	5	4	9
US0014	Aaronson	1	2	3
US0015	Brand	4	4	8
US0016	Goldstein	0	1	1
	Makarowski	2	2	4
TOTAL		191	193	384

* multiple investigator codes assigned

sponsor's table modified, NDA Vol. 1.101, p. 8-24188

Fifty-three investigators enrolled a total of 384 patients in the prophylaxis phase of the study. Fifteen centers each enrolled 10 or more patients (about 60% of total patients). The 15 U.S. sites enrolled a total of 115 patients in this phase.

Study 269: Demographic and Baseline Characteristics of the Study Population

	Diclofenac 50mg + Placebo b.i.d.-t.i.d. (n=191)	Diclofenac 50mg + Misoprostol 200mcg b.i.d.-t.i.d. (n=192)
Age (years)		
mean	57.5	57.3
median	60.0	60.0
range		
Gender (%)		
male	30%	34%
female	70%	66%
Type of Arthritis (% of patients):		
Rheumatoid arthritis	52%	48%
Osteoarthritis	48%	51%
Rheumatoid Arthritis Disease Duration (years):		
mean	12.1	10.0
median	10	8
range		
Osteoarthritis Disease Duration (years):		
mean	9.0	10.3
median	6	8
range		
History of Current NSAID Use (years):		
mean	2.2	2.5
median	1	1
range		
Baseline Endoscopy Findings[a] gastric/duodenal (%):		
normal (score=0)	75% / 88%	72% / 91%
petechiae only[b] (score=1 or 2)	12% / 2%	9% / 1%
1-10 erosions (score =3-4)	13% / 9%	20% / 8%
>10 erosions (score=5)	0% / 0%	0% / 0%
oozing or intraluminal blood (score=6)	1% / 0%	0% / 0%
Ulcer (score=7)	1% / 1%	0% / 0%
Unknown	1% / 1%	0% / 0%

Global Assessment of UGI Symptoms, %[c]:		
none	45%	44%
mild	41%	45%
moderate	13%	10%
severe	1%	1%
unknown	1%	0%
total	100%	100%
Baseline Rheumatoid Arthritis Global Assessments, %[c]:		
none	1%	1%
mild	33%	49%
moderate	56%	43%
severe	10%	6%
unknown	0%	0%
total	100%	100%
Baseline Osteoarthritis Global Assessments, %[c]:		
none	1%	0%
mild	39%	23%
moderate	46%	63%
severe	14%	14%
unknown	0%	0%
total	100%	100%
Dosing Regimen at Week 6:		
b.i.d.	86 (45.0%)	100 (51.8%)
t.i.d.	96 (50.3%)	81 (42.0%)
unknown	9 (4.7%)	12 (6.2%)
Dosing Regimen Changed During Study (number of patients)	43	41

[a] findings at end of treatment period prior to maintenance period; also, note that definitions for lesions in this study are slightly different from those for Study 349.

[b] or coalescent intramucosal blood

[c] % = percent of patients

from sponsor's tables, NDA Vol. 1.101, pp. 8-24198, 8-24199, 8-24226 and 8-24227, 8-24231 and 8-24232, 8-24234 and 8-24235, and NDA Vol. 1.102, pp. 8-24531 through 8-24542

The treatment groups were well-matched for demographic features. Patients were about equally divided between those with rheumatoid arthritis and those with osteoarthritis. Patients averaged about 57 years of age. About 70% of patients were females. Most patients started the prophylactic phase of study with normal gastric and duodenal mucosa. Upper gastrointestinal symptom severity (UGI symptoms) were similar in both treatment groups. There was a trend toward less severe arthritis symptoms at baseline in the diclofenac +

placebo osteoarthritis patients as compared to the diclofenac + misoprostol osteoarthritis patients (p=0.0580); this tendency was less pronounced in the rheumatoid arthritis patients (p=0.1490).

It is not clear how many patients initially were assigned to each regimen (b.i.d. or t.i.d.). The patient data tabulations list "predominant regimen" for Week 6, Week 12, Week 18, Week 24, Week 36, and Week 52. For "Week 6" patients appeared about equally divided between the two regimens; however, about 5% of patients were missing this data. Forty-three diclofenac + placebo patients and 41 diclofenac + misoprostol patients appear to have changed regimen (from b.i.d. or vice versa) at some time during the 52-week study. Some patients had the regimen changed more than once. The initial change in most cases appears to have been from b.i.d. treatment to t.i.d. treatment (24 diclofenac + placebo patients and 27 diclofenac + misoprostol patients).

2. Disposition of Patients: Of the 384 patients enrolled in the maintenance phase of the study, 268 patients successfully completed 12 weeks of study participation. One-hundred thirty-eight successfully completed 52 weeks of study participation. Reasons for premature discontinuation of the 116 patients who failed to complete 12 weeks of the study are summarized in the table below:

Study 269: Reasons for Termination of Study Participation Prior to 12 Weeks

Reason	Number of Patients					
	Diclofenac 50mg + Placebo b.i.d.-t.i.d.			Diclofenac 50mg + Misoprostol 200mcg b.i.d.-t.i.d.		
	12 Wk Endo Done	12 Wk Endo Not Done	Total	12 Wk Endo Done	12 Wk Endo Not Done	Total
Enrolled	168	23	191	177	16	193
Completed	127	0	127	141	0	141
Discontinued:						
Lost-to-followup	2	8[a]	10	0	5	5
Protocol Noncompliance	1	5	6	3	6	9
Treatment Failure[a]	33	0	33	14	0	14
Adverse event	5	9[b]	14	19	5[c]	24
Death	0	1	1	0	0	0

[a] endoscopically confirmed clinically significant lesions

[a] one patient discontinued on day 91; [b] one patient discontinued on day 84, another on day 201; [c] one patient discontinued on day 95

reviewer's original table, based on datasets froms sponsor's CANDA submission and NDA Vol. 1.102, pp. 8-24573 through 8-24584

[Note: Endoscopy data from this study is not included in the sponsor's CANDA submission].

A greater proportion of adverse event withdrawals in the diclofenac/misoprostol group were endoscoped than in the diclofenac alone group (79% as compared to 34%).

3. **Efficacy Analysis**: Endoscopy results at 12 weeks are summarized in the table below. [Note: Endoscopy results for this study were not included in the sponsor's CANDA submission, so all the following tables are derived from the sponsor's tables in the study report]. Lesions are classified as clinically significant (scores of 5, 6, or 7 on the Revised Mucosal Grading Scale) or clinically insignificant (scores of 0, 1, 2, 3, or 4):

Study 269: Final Gastric and Duodenal Endoscopy Results

	Diclofenac 50mg + Placebo b.i.d.-t.i.d. (n = 191)	Diclofenac 50mg + Misoprostol 200mcg b.i.d.-t.i.d. (n = 193)
Number of Patients having final endoscopy (gastric/duodenal*):	168/167	177/177
Final Endoscopy Findings, gastric/duodenal (% of endoscoped):		
clinicallyinsignificant	86.3/91.6	94.9/96.0
clinically significant	13.7/8.4	5.1/4.0
Total	100/100	100/100

reviewer's original table, based on data in sponsor's table, NDA Vol. 1.101, pp. 8-24202

About 10% of patients (12% of diclofenac + placebo, 8% of diclofenac + misoprostol) did not undergo endoscopy at 12 weeks. For the patients who were endoscoped at 12 weeks, the final endoscopy findings were clinically insignificant in the vast majority of patients in both treatment groups. By the sponsor's analysis, the group receiving diclofenac and misoprostol had significantly fewer clinically significant lesions than did the group receiving diclofenac alone ($p = 0.011$). For duodenal lesions the difference between groups was not clinically significant ($p = 0.090$).

The following table summarizes the ulcer occurrence rates for the two treatment groups at Week 12. In this intent-to-treat analysis patients who have missing data (i.e., who did not have followup endoscopy) are assumed to have no ulcers.

Study 269: Ulcer Rates at Week 12 in the Various Treatment Groups (Intent-to-Treat Analysis)

	Number of Patients (%)	
	Diclofenac 50mg + Placebo b.i.d.-t.i.d. (n = 191)	Diclofenac 50mg + Misoprostol 200mcg b.i.d.-t.i.d. (n = 193)
Gastric Ulcer	19 (9.9%)	8 (4.1%)
Duodenal Ulcer*	14 (7.3%)	7 (3.6%)
Unknown	23 (12.0%)	16 (8.3%)

* pyloric channel ulcers are notspecifically mentioned in this protocol; the protocol specified that the antrum, corpus, and duodenum would be examined

reviewer's original table, from sponsor's table NDA Vol. 1.101 pp. 8-24209

The sponsor found a statistically significant difference between treatment groups in the incidence of gastric ulcers ($p = 0.030$) but not for duodenal ulcers ($p = 0.090$).

No analysis was done of ulcer rates separately for osteoarthritis patients and rheumatoid arthritis patients.

Ulcer rates at study completion (52 weeks) did not differ significantly in the two treatment groups ($p = 0.366$ for gastric ulcer; $p = 0.300$ for duodenal ulcer). About 13% of diclofenac + placebo patients and 8% of diclofenac + misoprostol patients had gastric ulcers; about 10% of diclofenac + placebo patients and 6% of diclofenac + misoprostol patients had duodenal ulcers. About 50% of randomized patients had follow-up endoscopy at study completion.

4. **Safety**: In this study 41.4% of diclofenac + placebo patients and 51.3% of diclofenac + misoprostol patients experienced adverse events during the prophylaxis phase. Events occurring in 2% or more of the patients in the diclofenac + misoprostol group were: abdominal pain (11.9% for diclofenac + misoprostol vs. 7.9% with diclofenac alone), diarrhea (9.8% vs. 7.3%), dyspepsia (9.3% vs. 4.7%), nausea (5.7% vs. 3.1%), upper respiratory tract infection (5.2% vs. 1.6%), arthritis aggravated (4.7% vs. 2.6%), headache (4.7% vs. 3.1%), influenza-like symptoms (4.1% vs. 1.6%), flatulence (3.6% vs. 1.0%), eructation (3.1% vs. 1.6%), vomiting (2.6% vs. 4.2%) and abnormal hepatic function (2.1% vs. 0.0%). When only the first 12 weeks of the study are considered. Adverse events were most commonly reported during the first 12 weeks of study. Most adverse events

(76% of diclofenac + misoprostol and 67% of diclofenac alone) were mild or moderate in severity. Events occurring in the diclofenac + misoprostol patients and considered to be serious included myocardial infarction*, eye inflammation*, severe vertigo, septic arthritis of an articficial hip*, perforated sigmoid diverticulum*, scheduled hip replacement, unstable angina, exacerbation of congestive heart failure, benign prostatic nodule, hernia repair, hypertensive crisis and possible stroke*, scheduled back surgery, and probable gasroeneteritis. [* patients discontinued from study due to event].

Two diclofenac + misoprostol patients and one diclofenac alone patient had post-menopausal bleeding and one additional diclofenac + misoprostol patient suffered pelvic inflammation.

Two placebo patients developed ulcers (1 gastric, 1 duodenal) that necessitated or prolonged a hospitalization. One diclofenac + misoprostol patient developed esophageal ulceration after 25 weeks on double-blind medication.

There were 3 deaths of patients while on study medication:

- Patient US0011-B804, a 72 year old man with osteoarthritis, hypertension, and ischemic heart disease on misoprostol 200mcg b.i.d. died of a myocardial infarction after about 12 weeks in the prophylaxis phase.
- Patient US0003-B924, a 64 year old woman with osteoarthritis, hypertension, recurrent bronchitis died of complications due to pneumonia after 5.5 months on diclofenac + placebo in the double-blind phase.
- Patient GR0001-B434, a 77 year old woman with a history of myocardial, endocardial, and valvular dysfunction who was randomized to diclofenac + placebo suffered myocardial infarction and verntricular fibrillation and expired after about 1 month on study medication.

A fourth patient, US0002-B910, an 80 year old man with osteoarthritis, osteoporosis, chronic obstructive lung disease, and chronic leg edema developed a pre-pyloric ulcer after 5 months of treatment with misoprostol 200mcg b.i.d. during the double-blind prophylaxis phase of the study and was withdrawn. He died about 6 weeks later due to fatal cardiopulmonary arrest. None of these deaths was judged by the investigator to be related to study medication.

With regard to clinical laboratory parameters, from 0-12 weeks, statistically significant shifts were observed for hematocrit (decrease), SGPT (increase), and BUN (increase) for the diclofenac alone group.

No statistically significant shifts were seen in any parameter for the diclofenac + misoprostol group; however, there was a statistically significant increase in mean SGPT from 24.513 to 29.598. Comparisons of "shift" results between treatment groups showed differences only for iron binding capacity at Week 24 and for hematocrit and hemoglobin at Week 52. In all these comparisons, none of the differences was considered clinically meaningful.

C. **Reviewer's Comments:** In this study the sponsor found significantly fewer patients with gastric ulcer in the group treated with diclofenac 50mg + misoprostol 200mcg as compared to the group treated with diclofenac 50mg + placebo. However, this study suffers from the design problem that though treatment assignment was randomized, dosing regimen (b.i.d. or t.i.d.) was not; therefore, interpretation of efficacy results is compromised.

There were no statistically significant differences between the two treatment groups with regard to incidence of duodenal ulcer at Week 12 or with regard to incidence of gastric ulcer or duodenal ulcer at the study's completion (52 Weeks).

Adverse events reported in this study were in keeping with the known adverse event profiles of misoprostol and diclofenac.

VI. **Protocol: NN2-94-02-352:** Double-Blind, Placebo-Controlled, Comparative Study of the Efficacy and Safety of Diclofenac 75mg BID, Diclofenac 50mg/Misoprostol 200mcg TID, and Diclofenac 75mg/Misoprostol 200mcg BID in Treating the Signs and Symptoms of Rheumatoid Arthritis (NDA Vol. 1.87, p. 8-17261 through 1.100, p. 8-24147)

[Note: Though this study did not involve endoscopy, I have reviewed it here because it is the only study other than Study 349 which was done in the United States and used the formulations the sponsor intends to market].

A. **Principal Investigators:** This study was carried out from July 21, 1994 through February 1, 1995 at sites in the United States and Canada. It involved a total of 20 principal investigators each of whom enrolled at least 1 subject. These investigators are listed below:

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** participated in Study NN2-94-02-349, different address

from sponsor's table, NDA Vol. 1.87, pp. 8-17306 through 8-17308

Thirteen of the 20 investigators also participated in the Protocol NN2-94-02-349 study of osteoarthritis.

B. **Objectives:** The primary objective of this study was to compare the efficacy of Arthrotec I TID versus diclofenac 75mg BID, Arthrotec II BID versus diclofenac 75mg BID, and to compare diclofenac 75mg BID versus placebo in treating the signs and symptoms of RA [rheumatoid arthritis]." Safety of the treatments also was to be assessed.

C. **Design:** This was a randomized, double-blind, placebo-controlled, parallel group comparison of the Arthrotec I and Arthrotec II versus diclofenac and diclofenac versus placebo for 12 weeks with regard to efficacy in relieving the signs and symptoms of rheumatoid arthritis. Randomization was unbalanced with a planned sample size of 90 for the diclofenac, Arthrotec I and Arthrotec II arms and 45 for the placebo arm.

D. **Subjects:** Subjects were to be 360 adult males or females having at least a 6 month history of adult onset rheumatoid arthritis as defined by American College of Rheumatology criteria (Arnett, FC et al. Arthr. Rheum. 31:315-324 (1988)) which are as follows:

The patient must have met at least 4 of the following 7 criteria, and criteria 1 through 4 must have been present for at least 6 weeks:

1. Morning stiffness: Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.

2. Arthritis of 3 or more joint areas: At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

3. Arthritis of hand joints: At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint.

4. Symmetric arthritis: Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

5. Rheumatoid nodules: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in justaarticular regions, observed by a physician.

6. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.

7. Radiographic changes: Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Female patients were to be of non-childbearing potential or have been using adequate contraception. Patients were to have a Functional Capacity Classification of I-III (see scale under Study 349 above) and the rheumatoid arthritis must have been stable (as measured by Functional Capacity Classification) for the preceding 30 days while receiving a single NSAID for at least one month immediately preceding the NSAID washout period (Screening

Visit). Patients must have had RA in the "flare state" within 3-14 days after discontinuing NSAID therapy. "Flare state" was defined as showing 3 of the following 5 criteria:

- increase of one or more grades in the Physician's Global Assessment of Arthritic Condition [See Study 349 above (I.F.) for scale],

- increase of 1 or more grades in the Patieint's Global Assessment of Arthritic Condition [See I.F. above for scale],

- increase of 2 or more joints in the Assessment of Joint Tenderness /Pain, [This assessment involved the evaluation of tenderness/pain in 68 joints (right and left sides) with tenderness/pain on palpation of each joint being graded as: 0 = none, 1 = positive response to questioning (tender), 2 = spontaneous response elicited (tender and winced), or 3 = withdrawal by patient on examination (tender, winced and withdrew)].

- increase of 2 or more joints in the Assessment of Joint Swelling, [This assessment involved the evaluation of swelling in 66 joints (right and left sides). Joints to be evaluated are the same as for the assessment of joint tenderness/pain except that the hips are excluded. Swelling is graded as: 0 = none, 1 = detectable synovial thickening without loss of bony contours, 2 = loss of distinctiveness of bony contours, and 3 = bulging synovial proliferation with cystic characteristics].

- 25% increase in Duration of Mornining Stiffness (recorded in minutes) [This is defined as the interval between the time of awakening and the time when the patient is as limber as he or she will be for that day]..

from sponsor's table, NDA Vol. 1.87, pp. 8-17507 and 8-17514 and 17515

Criteria for exclusion were as follows:

1. Arthritis other than adult RA as the primary arthritis or any other inflammatory joint disease.

2. Active gastrointestinal disease, chronic or acute renal or hjepatic disorder, or significant coagulation defect,

3. Active esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to NSAID washout period.

4. Active malignancy or history of malignancy, other than surgically treated basal cell carcinoma. Patients with history of surgically treated cancer with no remission in 5 years are eligible for study participation.

5. Use of any of the following medicaitons: corticosteroids doses greater than 10mg oral prednisone [intraarticular and intramuscular injections may be used up to 6 weeks prior to NSAID washout period], gold salts, penicillamine, methotrexate doses greater than 15mg/wk, antimalarials, azathioprine, or sulfasalazine.

6. Use of any NSAID (including aspirin) within 3 days prior to the Baseline Arthritis Assessments or any analgesic with in the 24 hours prior to Baseline Arthritis Assessments.

7. Liver enzymes greater than 1.5 times the upper limit of normal within 7 days prior to first dose of study medication.

8. Receipt of any investigational medication within 30 days prior to first dose of study medication.

9. Known hypersensitivity to diclofenac or other NSAIDs, or misoprostol or other prostaglandins.

10. Prior admission to this study.

All patients gave written informed consent prior to study participation.

E. **Study Drugs:** Patients were to be randomized to Arthrotec I (diclofenac 50mg/misoprostol 200mcg) TID, Arthrotec II (diclofenac 75mg/misoprostol 200mcg) BID, diclofenac 75mg BID or placebo. The Arthrotec formulations used in this study were the same as used in Study 349 (aqueous-based enteric coated formulations the sponsor intends to market). However, the diclofenac formulation was a plain white tablet consisting of a placebo mantle in a fixed combination with 75mg diclofenac sodium enteric coated core; Placebo tablets were identical in appearance to the diclofenac/misoprostol and diclofenac tablets.

All patients received three bottles of study medication. They were instructed to take one tablet from the "morning dose" bottle with their morning meal, one tablet from the "noon dose" bottle with their noon meal and one tablet from the "evening dose" bottle with their evening meal.

F. **Study Plan:** At the screening visit (3-14 days prior to baseline visit) Arthritis Assessments were performed. These included Assessment of Joint Tenderness/Pain, Assessment of Joint Swelling, Physician's Global Assessment of Arthritic Condition, Functional Capacity, Patient's Global Assessment of Arthritic Condition, Duration of Morning Stiffness, and Patient Assessment of Arthritis Pain [measured on a 0 to 10cm visual analog scale, 0 = no pain, 10 = most severe pain]. Immediately after these assessments were completed, patients were instructed to discontinue their current NSAID therapy and to notify the investigator when flare symptoms began.

Patients were to return for a Baseline Visit 3 to14 days after screening. At this time patients who met the criteria for rheumatoid arthritis in the "flare state" as described under "C." above underwent Baseline Arthritis Assessments (repeat of the 7 assessments done at screening), had complete medical history taken, and physical examination done, completed the Patient's Health Assessment Questionnaire, a health survey, and had clinical laboratory tests done. Laboratory tests included: WBC, hematocrit, platelet count, erythrocyte sedimentation rate, serum creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, and serum pregnancy test if applicable.

Qualified patients were randomly assigned to receive Arthrotec I t.i.d., Arthrotec II b.i.d., diclofenac 50mg t.i.d. or placebo t.i.d. beginning not more than 7 days after Baseline assessments and continuing for 12 weeks. All patients took 3 study drug doses each day (See "I.F." above). Patients were to record information on symptoms, concurrent medications, and adverse events on diary cards.

The sponsor's schedule of study events is shown below:

Study 352: Schedule of Observations and Procedures

	Screening	Baseline	Week 2	Week 6	Week 12 (or final)
Discontinue NSAID	X				
Medical History		X			
Physical Exam		X			X
Arthritis Assessments	X (a)	X	X	X	X
ESR		X	X	X	X
Laboratory Tests		X	X	X	X
Serum Pregnancy Test		X (b)			
Dispense Study Med		X	X	X	
Tablet counts			X	X	X
HAQ and QL		X	X	X	X

(a) Screening arthritis assessment data will be recorded on worksheets to be retained at site.
(b) A serum pregnancy test will be performed on all females of childbearing potential within 72 hours prior to dosing.

sponsor's table, NDA Vol. 1.87, p. 8-17428

Concomitant medications were to be recorded. Patients were specifically prohibited from using antineoplastics (other than methotrexate or azathioprine as antiarthritic therapy), NSAIDs (other than aspirin for non-arthritic reasons), intra-articular injections of corticosteroids, misoprostol, and analgesics. In addition, increases in doses of antiarthritic regimens, including corticosteroids, were prohibited.

G. **Compliance:** Compliance with medication dosing was assessed by pill counts at the Week 2, Week 6 and Week 12 (or final) visits. Compliance with study medication was defined as follows: (a)for the Week 2 visit, took at least 70% of the doses prescribed from day one through the Week 2 visit, (b)for the Week 6 visit, took at least 70% of the doses prescribed from the Week 2 visit through the Week 6 visit and at least 50% of the doses prescirbed from day one through the Week 2 visit; (c)for the Week 12 visit, took at least 70% of the doses prescribed from the Week 6 visit through the Week 12 visit and at least 50% of the doses prescribed from the Week 2 visit through the Week 6 visit and at least 505 of the doses prescribed from day one through the Week 2 visiit; and for each visit could not have missed all study medication on more than two consecutive days since the previous visit.

H. **Monitoring of Adverse Events:** Adverse events occurring during the study were to be recorded on the case report forms at each study visit. Information about the seriousness, severity, duration, outcome and any intervention were to be recorded.

I. **Efficacy Parameters:** Primary efficacy parameters were:
- Physician's Global Assessment of Arthritic Condition
- Patient's Global Assessment of Arthritic Condition
- Assessment of Joint Tenderness/Pain, and
- Assessment of Joint Swelling.

These parameters were to be evaluated for the Intent-to-treat and the evaluable population.

J. **Statistical Analysis:** Sample size was calculated (using arc sine transformation) as adequate to detect a difference between an improvement rate of 30% in the placebo group and a 70% improvement rate in the diclofenac group.

Chi square testing was used to compare the distributions of patients whose Physician's and Patient's Global Assessment of Arthritic Condition were: "Much Improved, Improved, Unchanged, Worsened, or Much Worsened". Statistical testing was 2-sided and Hochberg's procedure was to be used for planned pairwise comparisons.

K. **Amendments:** This protocol had one amendment which was made 1 day prior to the enrollment of any patients. This amendment did the following: specified number of study centers, reworded the objective slightly (changed "antiarthritic efficacy" to "efficacy"), specified that oral and intramuscular gold salts were prohibited, changed time of allowed use of intraarticular and intramuscular corticosteroid injections from up to 30 days prior to NSAID washout period to up to 6 weeks prior to the NSAID washout period, changed allowed liver enzyme abnormality from not more than 1.2X upper limit of normal to 1.5X upper limit of normal, added serum pregnancy testing at final visit, specified that artificial joints were not to be assessed, clarified restrictions on analgesic use during the study, and changed case report form worksheets to incorporate the protocol changes.

L. **Results:**

1. **Enrollment and Baseline Characteristics of Patients:** A total of 380 patients were randomized. Numbers of patients enrolled were reasonably even across the 20 centers. Patient enrollment by center is shown in the following table:

Study 352: Enrollment of Patients by Center

Investigator No.	Investigator	Placebo	Diclofenac 75mg	Diclofenac 50mg/Misoprostol 200mcg	Diclofenac 75mg/Misoprostol 200mcg	Total
CA0019	Choquette	3	4	5	5	17
CA0020	Bensen	2	4	4	4	14
US0001	Caldwell	5	10	10	10	35
US0002	McMillen	2	5	6	6	19
US0003	Ettinger	1	2	2	4	9
US0004	Lee	2	3	4	4	13
US0005	Makarowski	3	4	5	6	18
US0006	Weaver	3	6	6	6	21
US0007	Wiesinhutter	4	9	8	8	29
US0008	Sikes	3	4	5	5	17
US0009	Halla	3	5	5	5	18
US0010	Burch	4	8	8	8	28
US0011	Fleischmann	2	4	5	4	15
US0012	Lies	2	4	2	3	11
US0013	Jones	2	4	4	4	14
US0014	Roth	4	11	8	9	32
US0015	Marker	2	3	4	4	13
US0016	Trapp	4	8	8	7	27
US0017	Lisse	2	5	4	6	17
US0018	Skosey	2	4	4	3	13
TOTAL		55	107	107	111	380

sponsor's table modified, NDA Vol. 1.87, pp. 8-17306 through 8-17308

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Demographic and baseline features of the study population are shown in the table below:

Study 352: Demographic and Baseline Characteristics of the Study Population

	Placebo (n=55)	Diclofenac (n=107)	Diclofenac 50mg/ Misoprostol 200mcg (n=107)	Diclofenac 75mg/ Misoprostol 200mcg (n=111)
Age (years)				
mean	57.7	56.2	55.2	57.0
median	58	56	56	58
range				
Race (%)				
Caucasian	91%	88%	90%	91%
Black	7%	3%	3%	7%
Oriental	0%	1%	0%	0%
Other	2%	8%	7%	2%
Gender (%)				
male	31%	29%	19%	28%
female	69%	71%	81%	72%
Rheumatoid Arthritis Disease Duration (years):				
mean				
median	12.0	11.8	10.8	11.5
range	10	9	9	10
Baseline Rheumatoid Arthritis Physician's Global Assessment, %*:				
very good	0%	0%	0%	0%
good	5%	10%	7%	11%
fair	53%	42%	40%	46%
poor	33%	38%	42%	35%
very poor	9%	9%	11%	7%
total	100%	100%	100%	100%
Baseline Rheumatoid Arthritis Patient's Global Assessment, %*:				
very good	0%	0%	0%	0%
good	9%	8%	9%	11%
fair	40%	38%	35%	37%
poor	33%	43%	42%	36%
very poor	18%	10%	14%	15%
total	100%	100%	100%	100%

* % = percent of patients

from sponsor's tables, NDA Vol. 1.87, pp. 8-17317 and 8-17320

The treatment groups were well-matched for demographic features and baseline assessments. Patients averaged about 57 years of age and about 72% of patients were females. Most patients started the

study in fair or poor arthritic condition based on Physician and Patient Global Assessments. Gastrointestinal symptoms were not assessed. Patients history of NSAID use was not summarized.

2. **Disposition of Patients**: Of the 380 patients enrolled in the study, 248 patients completed 12 weeks of study participation. Reasons for premature discontinuation are summarized in the table below:

Study 352: Disposition of Patients

	Number of Patients (%)			
	Placebo	Diclofenac 75mg b.i.d.	Arthrotec I t.i.d.	Arthrotec II b.i.d.
Randomized	55	107	107	111
Completed	32 (58.2%)	78 (72.9%)	67 (62.6%)	71 (64.0%)
Discontinued Prematurely:				
Lost-to-followup	0	0	1	2
Protocol deviation	2	4	5	4
Pregnancy	0	0	0	0
Treatment Failure	21	15	16	23
Adverse sign or symptom	0	10	18	11
Death	0	0	0	0
Unknown	0	0	0	0

sponsor's table, NDA Vol. 1.87, p. 8-17311

Premature discontinuations were more numerous among Placebo patients than in the other groups. In the placebo group 38.2% of patients discontinued because of treatment failure, as compared to 14.0%, 15.0%, and 20.7% of diclofenac alone, Arthrotec I, and Arthrotec II patients, respectively. No placebo patients discontinued because of adverse events. However, 9.3% of diclofenac patients, 16.8% of Arthrotec I patients, and 9.9% of arthrotec II patients discontinued because of adverse events.

3. **Efficacy Analysis**: For the primary efficacy parameters (Physician's Global Assessment, Patient's Global Assessment, Assessment of Joint Tenderness/Pain, and Assessment of Joint Swelling), change from baseline was compared among the groups at Week 2, Week 6, and Week 12 followup. The definitions and categories of improvement used in the sponsor's analyses were somewhat different from those specified in the protocol. The main efficacy tables in the sponsor's study report compared mean change from baseline in the efficacy parameters between treatment groups.

The sponsor found no statistically significant differences between diclofenac alone and either Arthrotec I or Arthrotec II with regard to mean change in any of the 4 primary efficacy parameters. Also, there were no statistically significant differences between diclofenac alone and either Arthrotec I or Arthrotec II in the sponsor's categorical analyses (numbers of patients improved, unchanged or worsened) for these efficacy parameters, except for diclofenac alone compared to Arthrotec I at Week 12 ($p=0.047$) where there were more diclofenac patients improved than Arthrotec I patients improved. P-values for during the study pairwise comparisons of the treatments for these parameters are given in the following table:

Study 352: Efficacy Comparisons (for Treatment of Arthritis Symptoms) (Intent-to-Treat Population)

	Arthrotec I TID vs. Placebo			Arthrotec II BID vs. Placebo			Arthrotec I TID vs. Arthrotec II BID		
	Week 2	Week 6	Week 12	Week 2	Week 6	Week 12	Week 2	Week 6	Week 12
Physician's Global Assessment:									
mean change from baseline	0.010	0.072	0.025	0.000	0.029	0.089	0.127	0.651	0.501
improved/worsened by score of 1 or more	0.010	0.224	0.107	0.001	0.121	0.543	0.589	0.463	0.444
improved by score of 2 or more	0.030	0.096	0.049	0.015	0.271	0.238	0.654	0.599	0.567
Patient's Global Assessment:									
mean change from baseline	0.044	0.441	0.390	0.000	0.162	0.317	0.055	0.446	0.868
improved/worsened by score of 1 or more	0.262	0.734	0.554	0.014	0.306	0.462	0.305	0.584	0.920
improved/worsened by score of 2 or more	0.091	0.468	0.529	0.052	0.462	0.337	0.577	0.990	0.546
Tender/Painful Joints Score:									
mean change from baseline	0.003	0.183	0.101	0.001	0.003	0.003	0.516	0.043	0.097
improved/worsened	0.002	0.205	0.133	0.000	0.082	0.008	0.759	0.441	0.013
Swollen Joints Score:									
mean change from baseline	0.024	0.256	0.288	0.002	0.014	0.024	0.277	0.107	0.147
improved/worsened	0.779	0.250	0.601	0.104	0.266	0.212	0.159	0.354	0.555

reviewer's orginal table based on information in sponsor's tables, NDA Vol. 1.87, pp. 8-17328 through 8-17336 and Vol. 1.99, pp. 8-23489 through 8-23506

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By these results, neither Arthrotec formulation appeared to perform consistently well throughout the 12 weeks of the study. Results with both Arthrotec I and Arthrotec II were best for the first 2 weeks and were spotty thereafter. Arthrotec I and Arthrotec II were indistinguishable; statistically significant difference between the two formulations were seen only for mean change in tender/painful joint score at Week 6 and for patients improved/worsened with regard to tender/painful joints score at Week 12.

4. **Safety:** During this trial 47.3% of placebo patients, 69.2% of diclofenac alone patients, 76.6% of Arthrotec I patients and 73.9% of Arthrotec II patients experienced adverse events. The most frequent events (incidence $\geq$ 5%) in any treatment group are listed in the following table:

Study 352: Most Frequent Adverse Events

Event	Number of Patients (%)			
	Placebo (n=55)	Diclofenac 75mg b.i.d. (n=107)	Arthrotec I t.i.d. (n=107)	Arthrotec II b.i.d. (n=111)
Dyspepsia	4 (7.3%)	21 (19.6%)	24 (22.4%)	23 (20.7%)
Diarrhea	3 (5.5%)	14 (13.1%)	27 (25.2%)	20 (18.0%)
Abdominal pain	4 (7.3%)	18 (16.8%)	29 (27.1%)	19 (17.1%)
Headache	13 (23.6%)	16 (15.0%)	18 (16.8%)	17 (15.3%)
Nausea	3 (5.5%)	9 (8.4%)	10 (9.3%)	14 (12.6%)
Flatulence	1 (1.8%)	5 (4.7%)	10 (9.3%)	10 (9.0%)
Sinusitos	2 (3.6%)	5 (4.7%)	3 (2.8%)	7 (6.3%)
Upper respiratory tract infection	1 (1.8%)	9 (8.4%)	13 (12.1%)	6 (5.4%)
Vomiting	1 (1.8%)	4 (3.7%)	6 (5.6%)	6 (5.4%)
Insomnia	0 (0.0%)	3 (2.8%)	0 (0.0%)	6 (5.4%)
Dizziness	0 (0.0%)	3 (2.8%)	4 (3.7%)	5 (4.5%)
Pharyngitis	1 (1.8%)	3 (2.8%)	4 (3.7%)	5 (4.5%)
Rash	0 (0.0%)	6 (5.6%)	5 (4.7%)	2 (1.8%)

from sponsor's table, NDA Vol. 1.87, pp. 8-17369 through 8-17372

Percentages of patients withdrawing from the study prematurely due to adverse events were 0 (0%) placebo patients, 10 (9.3%) of diclofenac patients, 18 (16.8%) of Arthrotec I patients, and 11 (9.9%) of Arthrotec II patients. Of these adverse event withdrawals, all except 3 diclofenac patients, 2 Arthrotec I patients and 2 Arthrotec II patients discontinued at or before 6 weeks on study medication. There were no statistically significant differences between active treatments in proportions of patients discontinuing due to adverse events. Major reasons for withdrawal due to adverse events included abdominal pain (3 diclofenac patients, 6 Arthrotec I patients, and 3 Arthrotec II patients), diarrhea (2 Arthrotec I patients and 4 Arthrotec II patients), dyspepsia, nausea, and/or vomiting.

Serious events occurring during this study included infectious colitis in a 64 year old woman on Arthrotec I with a history of steroid dependent rheumatoid arthritis; cholecystitis and cholecystectomy in a 33 year old woman on Arthrotec II with rheumatoid arthritis and obesity; treatment of Pasturella infected cat bite wound in a 44 year old woman on Arthrotec I; buinonectomy and pan-metatarsal head resection of the left foot in a 48 year old woman on Arthrotec I with steroid-dependent rheumatoid arthritis and osteoarthritis; cerebrobvascular accident in a 58 year old man on Arthrotec II with history of rheumatoid arthritis, insulin dependent diabetes mellitus, left ventricular hypertrophy, tobacco abuse and alcohol abuse; and excision of a basal cell carcinoma in a 71 year old man on Arthrotec I. None of these events was judged to be related to the study medication.

No patients died during this study; however, two patients suffered myocardial infarction and died within several weeks of completing the study. The first, a 60 year old man on Arthrotec I with a history of congestive heart failure, previous myocardial infarction, coronary vascular disease (status post CABG), and elevated cholesterol was discontinued from the study after 6 weeks because of diarrhea and dehydration. About a month later he suffered a myocardial infarction and died. The second patient, a 62 year old man on diclofenac with a history of rheumatoid arthritis, arteriosclerotic cardiac disease, diabetes mellitus and gastric ulcers completed the study and 3 days later suffered a myocardial infarction and subsequently died. Neither of these deaths was considered related to the study medication.

Considering the laboratory values, hematocrit decreased from baseline over the course of the study in the active treatment groups (particularly in the diclofenac and Arthrotec I groups). All treatment groups showed slight increases in AST (SGOT) and ALT (SGPT), slight increases in platelet counts, and slight decreases in bilirubin at some time during the study as compared to baseline. There was a slight increase in alkaline phosphatase and ESR with Arthrotec I during this study. There was a slight increase in serum creatinine with diclofenac alone and with Arthrotec II during this study. These changes were not clinically meaningful.

Two patients on diclofenac and 1 patient on Arthrotec I experienced menstrual cramps. Three patients on Arthrotec I and 1 patient on diclofenac experienced heavy menses or unexpected vaginal bleeding.

Two patients, a 63 year old man on diclofenac and a 64 year old man on Arthrotec I experienced abdominal cramps and rectal bleeding while on study medication. The bleeding resolved with continued study

medication but one patient withdrew because of continued abdominal cramps.

M. **Reviewer's Comments:** Because endoscopy was not done as part of this clinical trial, this study does not contribute information on the effectiveness of Arthrotec (diclofenac/misoprostol) in preventing gastric or duodenal lesions.

The rates of premature discontinuation of patients in all treatment groups in this study in rheumatoid arthritis patients were somewhat greater in this study of rheumatoid arthritis patients than was seen in osteoarthritis study 349. However, Study 349 had a treatment duration of 6 weeks while in this study, treatment was for 12 weeks. Rates of premature withdrawal for Study 349 and for Study 352 (total and at 6 weeks) due to any reason and due to adverse events are summarized in the table below.

Premature Discontinuation Rates for Study 349 (Osteoarthritis Patients) and Study 352 (Rheumatoid Arthritis Patients)

	Percent of Patients					
	Study 349		Study 352			
	final (6 weeks)		(6 weeks)		final (12 weeks)	
	total withdrawals	adverse event withdrawals	total withdrawals	adverse event withdrawals	total withdrawals	adverse event withdrawals
Placebo	23.1%	6.6%	34.5%	0.0%	41.8%	0.0%
Diclofenac 75mg b.i.d.	18.2%	13.0%	17.8%	6.5%	27.1%	9.3%
Diclofenac 50mg/Misoprostol 200mcg t.i.d. (Arthrotec I)	13.8%	9.2%	34.6%	15.0%	37.4%	16.8%
Diclofenac 75mg/Misoprosotol 200mcg b.i.d. (Arthrotec II)	18.9%	13.1%	26.1%	8.1%	36.0%	9.9%

reviewer's original table

Still, in this study most patients who discontinued (either due to adverse events or due to other reasons), did so prior to 6 weeks. In the placebo group, 19/23 withdrawals dicontinued at or before 42 days; in the diclofenac alone group, 19/29; in the Arthrotec I group, 37/40; and in the Arthrotec II group, 29/40. At 6 weeks in Study 352, there appeared to be a greater proportion of placebo, Arthrotec I patients and Arthrotec II patients discontinued prematurely than in Study 349. This may suggest that symptoms of arthritis may be more severe and more difficult to control and/or that these patients may be more susceptible to adverse effects of the diclofenac/misoprostol combination therapies tested in these studies. However, the prepature discontinuation rate for diclofenac alone in the rheumatoid arthritis patients (Study 352) was similar to that in the osteoarthritis patients (Study 349).

The adverse events reported in this study were consistent with labeled side effects for diclofenac and misoprostol.

SAFETY:

The safety database for Arthrotec consists of a total of 34 clinical studies in which either the fixed combination diclofenac/misoprostol tablet was given or diclofenac and misoprostol were given concurrently. A total of 5109 subjects/patients received either Arthrotec (n=3582) or diclofenac + misoprostol (n=1527)

Adverse Events Occurring at an Incidence of 1% or Greater in Patients Treated with Arthrotec in Phase III Studies

	Placebo	Diclofenac	Arthrotec
Number Randomized	146	1692	2168
Number Dosed	146	1691	2184
Number with Any Event	100 (68.5%)	847 (50.1%)	1357 (62.1%)
Events:			
Abdominal Pain	19 (13.0)	255 (15.1)	463 (21.2)
Diarrhea	12 (8.2)	180 (10.6)	409 (18.7)
Dyspepsia	39 (26.7)	185 (10.9)	314 (14.4)
Nausea	10 (6.8)	105 (6.2)	239 (10.9)
Flatulence	9 (6.2)	62 (3.7)	200 (9.2)
Headache	32 (21.9)	134 (7.9)	171 (7.8)
Gastritis	13 (8.9)	85 (5.0)	76 (3.5)
Vomiting	2 (1.4)	36 (2.1)	68 (3.1)
Dizziness	6 (4.1)	54 (3.2)	61 (2.8)
Constipation	3 (2.1)	48 (2.8)	56 (2.6)
Upper Respirstory Tract Infection	2 (1.4)	38 (2.2)	42 (1.9)
Eructation	0 (0.0)	9 (0.5)	35 (1.6)
Esophagitis	2 (1.4)	11 (0.7)	34 (1.6)
Pharyngitis	3 (2.1)	25 (1.5)	34 (1.6)
Duodenitis	8 (5.5)	30 (1.8)	32 (1.5)
Rhinitis	6 (4.1)	20 (1.2)	32 (1.5)
Rash	2 (1.4)	20 (1.2)	31 (1.4)
Influenza-like Symptoms	0 (0.0)	26 (1.5)	27 (1.2)
Pain	8 (5.5)	11 (0.7)	26 (1.2)
Back Pain	5 (3.4)	17 (1.0)	25 (1.1)
Sinusitis	4 (2.7)	12 (0.7)	24 (1.1)
Insomnia	0 (0.0)	16 (0.9)	22 (1.0)
Pruritus	1 (0.7)	16 (0.9)	22 (1.0)
Gastric ulcer	2 (1.2)	31 (1.8)	21 (1.0)

sponsor's table, NDA Vol. 1.125, p. 8-35212 and 8-35213

The organ systems having most adverse events in the diclofenac/misoprostol patients were the gastrointestinal system, central and peripheral nervous system disorders, body as a whole disorders and respiratory system disorders. Significantly more diclofenac/misoprostol patients than diclofenac alone patients reported gastrointestinal events (51.5% of Arthrotec patients, 37.9% of diclofenac alone patients; $p<0.001$), reproductive disorders, female (2.6% of Arthrotec patients, 1.2% of diclofenac alone patients; $p<0.030$), and musculo-skeletal system disorders (2.3% of Arthrotec patients, 1.3% of diclofenac alone patients; $p<0.023$). For specific adverse events, significantly more diclofenac/misoprostol patients than diclofenac alone patients reported abdominal pain (21.2% of Arthrotec patients, 15.1% of diclofenac alone patients; $p<0.001$), diarrhea (18.7% of Arthrotec patients, 10.6% of

diclofenac alone patients; $p<0.001$), dyspepsia (14.4% of Arthrotec patients, 10.9% of diclofenac alone patients; $p=0.002$), nausea (10.9% of Arthrotec patients, 6.2% of diclofenac alone patients; $p<0.001$), flatulence (9.2% of Arthrotec patients, 3.7% of diclofenac alone patients; $p<0.001$), eructation (1.6% of Arthrotec patients, 0.5% of diclofenac alone patients; $p=0.002$), and menorrhagia (0.9% of female Arthrotec patients, 0.1% of diclofenac alone female patients; $p=0.019$). In the coadministration trials, the incidence of female reproductive disorders was somewhat higher in both the diclofenac + misoprostol patients (3.6%) and diclofenac alone patients (1.5%) than in the fixed combination trials, but generally the types and frequencies of adverse events were similar in these studies.

Incidences of female specific adverse events are shown in the table below :

Female Specific Adverse Events in Arthrotec Patients as Compared to Diclofenac and Placebo Patients

	Placebo	Diclofenac	Arthrotec
Number of Female Patients Dosed	100	923	1294
Events:			
Menorrhagia	0 (0.0)	1 (0.1)	11 (0.9)
Intermenstrual bleeding	0 (0.0)	3 (0.3)	7 (0.5)
Menstrual disorder	0 (0.0)	1 (0.1)	7 (0.5)
Vaginitis	1 (1.0)	2 (0.2)	5 (0.4)
Vaginal hemorrhage	0 (0.0)	1 (0.1)	4 (0.3)
Breast pain, female	1 (1.0)	1 (0.1)	2 (0.2)
Leukorrhea	0 (0.0)	0 (0.0)	2 (0.2)
Dysmenorrhea	0 (0.0)	2 (0.2)	1 (0.1)
Breast enlargement	0 (0.0)	1 (0.1)	0 (0.0)
Breast fibroadenosis	0 (0.0)	1 (0.1)	0 (0.0)
Breast neoplasm malignant female	0 (0.0)	1 (0.1)	0 (0.0)
Mastitis acute female	0 (0.0)	1 (0.1)	0 (0.0)

from sponsor's table, NDA Vol. 1.125, pp. 8-35213 through 8-35221

More Arthrotec patients than diclofenac patients had episodes of unexpected vaginal bleeding (e.g., intermenstrual bleeding, menorrhagia, vaginal hemorrhage).

For the different Arthrotec doses the following table summarizes instances where statistically significant differences between Arthrotec and diclofenac alone were seen:

Statistically Significant Differences between Arthrotec and Diclofenac in Adverse Event Rates by Body System and Dose

Body System	Number of Patients (%)		P-Value
	Arhrotec	Diclofenac	
Arthrotec 50 BID vs. Diclofenac 50mg BID:			
Gastrointestinal system disorders	186 (47.6%)	51 (28.2%)	<0.001
Skin and Appendages Disorders	11 (2.8%)	0 (0.0%)	0.020
Vision Disorders	2 (0.5%)	5 (2.8%)	0.035
Arthrotec 50 TID vs. Diclofenac 50mg TID:			
Gastrointestinal System Disorders	327 (47.3%)	79 (18.9%)	<0.001
Central and Peripheral Nervous System Disorders	68 (9.8%)	14 (3.3%)	<0.001
Respiratory System Disorders	63 (9.1%)	15 (3.6%)	<0.001
Body as a Whole - General Disorders	49 (7.1%)	6 (1.4%)	<0.001
Psychiatric Disorders	23 (3.3%)	5 (1.2%)	0.030
Autonomic Nervous System Disorders	12 (1.7%)	1 (0.2%)	0.039
Metabolic and Nutritional Disorders	9 (1.3%)	0 (0.0%)	0.016
Arthrotec 50 BID-TID vs. Diclofenac 50mg BID-TID:			
Gastrointestinal system disorders	388 (51.7%)	317 (42.0%)	<0.001
Respiratory System Disorders	35 (4.7%)	55 (7.3%)	0.038
Reproductive Disorders, Female	16 (3.0%)	2 (0.4%)	0.001
Hearing and Vestibular Disorders	2 (0.3%)	10 (1.3%)	0.038
Arthrotec 50 QID vs. Diclofenac 50mg QID:			
Gastrointestinal System Disorders	29 (43.9%)	19 (24.7%)	0.021

from sponsor's tables, NDA Vol. 1.125, pp. 8-35186 through 8-35194

There were no significant differences between groups for these comparisons in incidence of liver and biliary system disorders. Among rheumatoid arthritis patients, 5 patients (4.7%)

on Arthrotec 50 t.i.d., 5 patients (4.5%) on Arthrotec 75 b.i.d., and 2 patients (0.6%) on Arthrotec 50 b.i.d.-t.i.d. had some liver/biliary system disoder as compared to 2 patients (1.9%) on diclofenac 75mg b.i.d. and 4 patients (1.2%) on diclofenac 50mg b.i.d.-t.i.d.

The following table summarizes for all randomized, double-blind, parallel clinical trials of Arthrotec the frequency of adverse events and the percentages of patients discontinued from study prior to completion. Studies 296, 298, 321, 349, 289, 292, 352, 269, 304, 305, and 306 are included in this analysis. Treatment durations ranged from 1-52 weeks with most patients being treated for 4-12 weeks.

Adverse Event Rates and Discontinuation Rates of Patients in the Arthrotec Clinical Trials

	Total Patients	Patients Completed (%)	Patients with Adverse Events (%)	Patients Withdrawing Due to Adverse Events (%)
Diclofenac 50mg BID	181	151 (83.4%)	78 (43.1%)	16 (8.8%)
Dliclofenac 50mg BID-TID	754	640 (84.9%)	413 (54.8%)	90 (11.9%)
Diclofenac 50mg QID	77	66 (85.7%)	30 (39.0%)	1 (1.3%)
Diclofenac 50mg TID	419	368 (87.8%)	117 (27.9%)	15 (3.6%)
Diclofeonac 75mg BID	261	204 (78.2%)	209 (80.1%)	30 (11.5%)
Diclofenac 50/Misoprostol 200 BID	391	331 (84.7%)	225 (57.5%)	43 (11.0%)
Dicifoenac 50/Misoprostol 200 BID-TID	750	610 (81.3%)	468 (62.4%)	95 (12.7%)
Diclofenac 50/Misoprostol 200 QID	66	48 (72.7%)	36 (54.5%)	11 (16.7%)
Diclofenac 50/Misoprostol 200 TID	693	562 (81.1%)	389 (56.1%)	59 (8.5%)
Diclofenac 75/Misoprostol 200 BID	286	213 (74.5%)	239 (83.6%)	33 (11.5%)
Naproxen 375mg BID	210	185 (88.1%)	157 (74.8%)	20 (9.5%)
Piroxicam 10mg BID	217	200 (92.2%)	151 (69.6%)	10 (4.6%)
Placebo	146	102 (69.9%)	100 (68.5%)	6 (4.1%)

reviewer's original table, based on data in sponsor's CANDA

Misoprostol doses in this study ranged from 200mcg b.i.d. to 200mcg q.i.d. Rate of premature discontinuation due to adverse events was a bit higher in the patients recieving 800mcg of misoprostol daily as compared to those receiving 400 or 600mcg of misoprostol daily. Rates of adverse event discontinuations did not appear to differ between diclofenac alone groups and groups receiving misoprostol 400-600mcg daily. In the overall database of the Arthrotec clinical trials, more patients on Arthrotec (all doses) than patients on diclofenac alone withdrew from study prematurely due to diarrhea (3.2% of Arthrotec patients, 1.2% of diclofenac patients) and due to abdominal pain (4.6% of Arthrotec patients, 2.5% of diclofenac patients). The general pattern of adverse events for patients $\geq$65 years of age was similar to that for patients aged <65 years; however, the database for the older patients was considerably smaller than for the younger patients (<65 years: 1627 Arthrotec patients and 1309 diclofenac patients; $\geq$65 years: 557 Arthrotec patients

and 382 diclofenac patients).

In the FDA Adverse Drug Reaction Information System (ADRIS) database there have been a total of 235 cases reported of adverse events in patients concurrently using diclofenac sodium and misoprostol. Seventy-two of these were judged to be serious and there were 14 deaths. The most frequent adverse events were: abdominal pain, 14.5% of patients; diarrhea, 11.1%; nausea, 8.9%; dyspepsia, 5.1%; flatulence, 4.7%; and chest pain, 4.3%. In the FDA ADRIS database, there were 112 (48%) patients reporting events classified as gastrointestinal; about 43% of patients with serious events had serious gastrointestinal events. There were 25 events related to possible liver toxicity. These were: SGOT (AST) increased, 7; liver function abnormal, 6; bilirubinemia, 4; SGPT (ALT) increased, 3; GGPT increased, 2; hepatitis, 2; and hepatomegaly, 1. [Note: In these counts, a patient may have more than one of the reported abnormalities].

The safety database generally supports the current labeling regarding adverse events of Voltaren and Cytotec. The data do not strongly suggest increased risk of hepatotoxicity or overall intolerability for Arthrotec 50 t.i.d. or Arthrotec 75 b.i.d. as compared to diclofenac alone. However, the possibility that some populations, such as rheumatoid arthritis patients, might be at increased risk cannot be ruled out with the current database. Post-marketing surveillance might be useful in exploring this possibility.

DISCUSSION:

Efficacy for Prevention of Gastric Ulcer and Duodenal Ulcer: Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg) and Arthrotec 75 (diclofenac 75mg/misoprostol 200mcg) are combination products consisting of two approved drugs having discrete therapeutic effects. Diclofenac is an NSAID which exerts an anti-inflamatory effect but does not provide protection of the gastrointestinal mucosa; misoprostol provides protection of the gastrointestinal mucosa but does not exert an antiniflammatory effect. Efficacy of Arthrotec can be established using either of two approaches: (1)Arthrotec 50 and Arthrotec 75 can be demonstrated to be effective in treating the signs and symptoms of arthritis and in preventing gastric ulcer and duodenal ulcer in 2 adequate and well-controlled clinical trials, or (2)the Arthrotec 50 and Arthrotec 75 that the sponsor intends to market can be demonstrated to be bioequivalent to marketed Cytotec + Voltaren with regard to bioabvailability of misoprostol and diclofenac. The current submission contains a patchwork of clinical efficacy data and bioequivalence results from studies using several different diclofenac/misoprostol combination formulations. The 'clinical trial approach' and the 'bioequivalence approach' to approval of Arthrotec 50 and Arthrotec 75 both are considered below:

Clinical Trial Approach: The sponsor has submitted 5 clinical trials in which the ulcer frequencies in patients treated with diclofenac/misoprostol combination were compared to the rates in patients treated with NSAID alone. All 5 trials were randomized, double-blind, and placebo-controlled. Some features and general results from these 5 studies are summarized in the following table:

Summay Table: Clinical Studies in Which Endoscopy Was Done

Study Number	Arthrotec Formulation	Patients Randomized	Treatments (duration)	Results
NN2-94-02-349		572 OA patients	Diclofenac 50mg/Misoprostol 200mcg t.i.d.; Diclofenac 75mg/Misoprostol 200mcg b.i.d.; Diclofenac 75mg b.i.d.; Placebo t.i.d. (6 weeks)	Statistically significant benefit of diclofenac 50mg/misoprostol 200mcg and diclofenac 75mg/misoprostol 200mcg over diclofenac alone in prevention of GU (p-values = 0.016 and 0.046, respectively) but not for DU (including pyloric channel ulcers (p-values = 0.637 and 0.060, respectively).
IN2-89-02-296		361 OA patients	Diclofenac 50mg/Misoprostol 200mcg b.i.d. or t.i.d.; Diclofenac 50mg/Placebo b.i.d. or t.i.d. (4 weeks)	Study not randomized to compare b.i.d. vs t.i.d. regimens. No benefit in GU or DU (p-values = 0.623 and 0.619, respectively).
IN2-90-02-321		643 OA patients	Diclofenac 50mg/Misoprostol 200mcg b.i.d.; Piroxicam 10mg b.i.d.; Naproxen 375mg b.i.d. (4 weeks)	Comparisons of diclofenac/misoprostol combination to other NSAIDs. No comparison with diclofenac alone. Statistically significant benefit of diclofenac/misoprostol over piroxicam and naproxen in preventing GU (p-values = 0.019 and 0.003, respectively) but only over piroxicam, but not naproxen, in preventing DU (p-vlaues = 0.007 and 0.493, respectively).
IN2-89-02-289		342 OA patients	Diclofenac 50mg/Misoprostol 200mcg b.i.d. or t.i.d.; Diclofenac 50mg/Placebo b.i.d. or t.i.d. (12 weeks)	(See my Medical Officer's Review of NDA 19-268 dated 3/14/96). Study not randomized to compare b.i.d. vs t.i.d. regimens. Statistically significant benefit of Diclofenac 50mg/Misoprostol 200mcg b.i.d./t.i.d. over Diclofenac 50mg/Placebo in prevention of duodenal ulcers (including pyloric channel ulcers) (1% vs 7%, p-value = 0.012). However, there was an imbalance in endoscopy rates between the two treatment groups which may have affected the result. No benefit in GU (p-value = 0.751).
EB2-87-02-269		384 OA patients	Diclofenac 50mg + Misoprostol 200mcg b.i.d. or t.i.d.; Diclofenac 50mg + Placebo b.i.d. or t.i.d. (52 weeks; (endoscopy at 0, 12, 24, and 52 weeks))	Study not randomized to compare b.i.d. vs t.i.d. regimens. Combination product not used, rather concurrent administration of alread marketed formulations of diclofenac and misoprostol. Only statistically significant benefit of diclo + miso in ulcer prevention in the ITT population was at 12 weeks in GU (p = 0.029). In the evaluable cohort, the sponsor found statistically significant results for GU at 12, 24, and 52 weeks (p-values = 0.002, 0.015, and 0.013, respectively). No statistically significant result was found for DU at any time.

GU = gastric ulcer;
DU = duodenal ulcer (including pyloric channel ulcers)

diclofenac 50mg/misoprostol 200mcg = Arthrotec I = Arthrotec 50;
diclofenac 75mg/misoprostol 200mcg = Arthrotec II = Arthrotec 75

reviewer's original table

Only one of these trials was well-designed for the demonstration of efficacy of a specific dose of Arthrotec in preventing gastrointestinal ulcers. This was Study 349. In this study osteoarthritis patients were endoscoped to verify that there were no ulcers or large numbers of erosions on study entry and then they were randomized to a specific dose and regimen of placebo, diclofenac alone, Arthrotec 50 or Arthrotec 75. Patients continued on the assigned regimen for 6 weeks without change in dosing frequency. At study completion (or dropout from study), patients again were endoscoped and ulcer frequencies among the treatment groups were compared. In three of the other studies (Studies 296, 289 and 269), though patients were randomized to treatment, the dosage regimen was not randomized but was set at b.i.d. or t.i.d. by the investigator depending on patients' symptoms; these studies also allowed changing from b.i.d. to t.i.d. dosing or vice versa during study and, in fact, many patients did change dosing regimen during the study. In the fifth study, Study 321, ulcer rates in patients treated with Arthrotec 50 b.i.d. were compared to the rates in patients treated with piroxicam or naproxen.

None of these clinical trials used the exact formulation of either Arthrotec 50 or Arthrotec 75 the sponsor intends to market. The Arthrotec formulations used in Study 349 and are most similar to the formulations proposed for marketing, differing only with regard to source of diclofenac and manufacturing site. [Note: Study 352 in rheumatoid arthritis patients also used these formulations, but endoscopy was not done during Study 352]. Ulcer occurrence rates for the all the treatment groups in these studies are tabulated below:

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Summary Table: Percentages of Patients Having Ulcers in Endoscopy Trials (Intent-to-Treat Population)

Study	Ulcer Rates number of patients/patients treated, (%)		
	Gastric Ulcer	Pyloric Channel Ulcer	Duodenal Ulcer
Study IN2-89-02-289 (12 weeks)			
Diclofenac 50mg/Misoprostol 200mcg b.i.d./t.i.d.*#	4/167 (2.4%)	1/167 (0.6%)	1/167 (0.6%)
Diclofenac 50mg/Placebo b.i.d./t.i.d.	6/175 (3.4%)	2/175 (1.1%)	10/175 (5.7%)
Study IN2-89-02-296 (4 weeks)			
Diclofenac 50mg/Misoprostol 200mcg b.i.d./t.i.d.*	1/178 (0.6%)	0/178 (0%)	2/178 (1.1%)
Diclofenac 50mg/Placebo b.i.d./t.i.d.	3/183 (1.6%)	2/183 (1.1%)	1/183 (0.5%)
Study IN2-90-02-321 (4 weeks)			
Diclofenac 50mg/Misoprostol 200mcg b.i.d.	3/216 (1.4%)	0/216 (0%)	0/216 (0%)
Piroxicam 10mg b.i.d.*	13/217 (6.0%)	2/217 (0.9%)	8/217 (3.7%)
Naproxen 375mg b.i.d.	15/210 (7.1%)	1/210 (0.5%)	1/210 (0.5%)
Study NN2-94-02-349 (6 weeks)			
Diclofenac 50mg/Misoprostol 200mcg t.i.d.	4/152 (2.6%)	0/152 (0%)	8/152 (5.3%)
Diclofenac 75mg/Misoprostol 200mcg b.i.d.	7/175 (4.0%)	3/175 (1.7%)	1/175 (0.6%)
Diclofenac 75mg b.i.d.*	15/154 (9.7%)	4/154 (2.6%)	7/154 (4.5%)
Placebo t.i.d.	2/91 (2.2%)	1/91 (1.1%)	0/91 (0%)
Study EB2-87-02-269:			
(12 weeks)			
Diclofenac 50mg + Misoprostol 200mcg b.i.d./t.i.d.	8/193 (4%)	*	7/193 (4%)
Diclofenac 50mg + Placebo b.i.d./t.i.d.	19/191 (10%)		14/191 (7%)
(24 weeks)			
Diclofenac 50mg + Misoprostol 200mcg b.i.d./t.i.d.	12/193 (6%)		9/193 (5%)
Diclofenac 50mg + Placebo b.i.d./t.i.d.	22/191 (12%)		16/191 (8%)
(52 weeks)			
Diclofenac 50mg + Misoprostol 200mcg b.i.d./t.i.d.	16/193 (8%)		11/193 (6%)
Diclofenac 50mg + Placebo b.i.d./t.i.d.	24/191 (13%)		19/191 (10%)

b.i.d./t.i.d. = dosage regimen b.i.d. or t.i.d. at discretion of the investigator based on patient symptoms.

* In Study 269 ulcers were classified as either gastric (corpus or antrum) ulcers or duodenal ulcers. Endoscopy results for this study appear not to be included in the sponsor's endodsopy database..

* One patient had both GU and DU; * Three patients had both GU and DU.

diclofenac 50mg/misoprostol 200mcg = Arthrotec I = Arthrotec 50;
diclofenac 75mg/misoprostol 200mcg = Arthrotec II = Arthrotec 75

reviewer's original table

In these calculations, patients who did not have final endoscopy done are considered to have had no ulcers. In none of these studies did gastric or duodenal ulcer rates exceed 10% during the first 12 weeks of study. With such low event rates, consideration of missing data may become important.

Statistical comparisons of ulcer rates with Arthrotec I (Arthrotec 50) and Arthrotec II (Arthrotec 75) versus NSAID alone are summarized in the table below. Numbers of patients missing final endoscopy results ("Unknown") are given for each treatment group.

Summary Table: Statistical Comparison of Ulcer Rates in Arthrotec Studies (Intent-to-Treat)

Study	Treatment									p-Values	
	Placebo	Diclofenac	Arthrotec I b.i.d.	Arthrotec I b.i.d.-t.i.d.	Arthrotec I t.i.d.	Arthrotec II b.i.d.	Diclofenac + Misoprostol	Piroxicam 10mg b.i.d	Naproxen 375mg b.i.d.	Arthro I vs. NSAID alone[f]	Arthro II vs.Diclo
Study 349[a]:											
GU	2/91	15/154			4/152	7/175				0.016	0.046
DU+PU	1/91	11/154			8/152	4/175				0.637	0.060
DU	0/91	7/154			8/152	1/175				0.798	0.028
PU	1/91	4/154			0/152	3/175				0.123	0.710
Unknown	11/91	15/154			10/152	16/175					
Study 296[b]:											
GU		3/183			0/178					0.087	
DU +PU		3/183			0/178					0.088	
DU		3/183			0/178						
PU		0/183			0/178						
Unknown		16/183			16/178						
Study 321[c]:											
GU			3/216					12/217	15/210	0.007;0.004	
DU+PU			0/216					10/217	3/210	0.002;0.001	
DU			0/216					8/217	2/210	ND	
PU			0/216					2/217	1/210	ND	
Unknown			16/216					13/217	12/210		
Study 289[d]:											
GU		6/175		4/167						0.571	
DU+PU		12/175		2/167						0.008	
DU		10/175		1/167						ND	
PU		2/175		1/167						ND	
Unknown		22/175		28/167							
Study 269[e]:											
GU		19/191					8/193			0.030	
DU+PU		---					---				
DU		14/191					7/193			0.090	
PU		----					---				
Unknown		23					16/193				

[a] Diclofenac 75mg b.i.d., Arthrotec I t.i.d., Arthrotec II b.i.d.
[b] Diclofenac 50mg b.i.d.-t.i.d.; Arthrotec I b.i.d.-t.i.d.
[c] Piroxicam 10mg b.i.d.; Naproxen 375mg b.i.d.; Arthrotec I b.i.d.
[d] Diclofenac 50mg b.i.d.-t.i.d; Arthrotec I b.i.d.-t.i.d.
[e] Diclofenac 50mg b.i.d.-t.i.d.; Diclofenac 50mg + Misoprostol 200mcg b.i.d.-t.i.d.
[f] For Study 321 the comparisons are versus piroxicam and versus naproxen

diclofenac 50mg/misoprostol 200mcg = Arthrotec I = Arthrotec 50; diclofenac 75mg/misoprostol 200mcg = Arthrotec II = Arthrotec 75

reviewer's original table

The results supporting Arthrotec 50 and Arthrotec 75 for prevention of gastric ulcer and prevention of duodenal ulcer are discussed below:

Gastric Ulcer:
(A) *Arthrotec 50:* In Study 349, significantly fewer patients on Arthrotec I t.i.d. had gastric ulcers than did patients on diclofenac alone ($p=0.016$), confirming the efficacy of misoprostol 200mcg t.i.d. in preventing gastric ulcers, an indication and dosing regimen for which approval of Cytotec already has been recommended. Also, in Studies 296, 289 and 269 Arthrotec I was compared to diclofenac alone. However, in these three studies the regimen (b.i.d. or t.i.d.) was not randomized so the efficacy analyses may not be valid. An apparent benefit of Arthrotec I over diclofenac was seen in Study 269 ($p=0.030$), but there was no apparent benefit of Arthrotec I in Studies 296 and 289 for prevention of gastric ulcers. In Study 321 a randomized regimen of Arthrotec I was used (b.i.d.) and a statistically significant benefit over comparator NSAIDs (piroxicam and naproxen) was demonstrated ($p=0.007$ and 0.004); however, the NSAIDs used for comparison did not include diclofenac so the relevance of these comparisons to Arthrotec I versus diclofenac is not clear.

Thus, the sponsor has one adequate and well-controlled study (Study 349) demonstrating efficacy of Arthrotec I given t.i.d. in preventing NSAID-induced gastric ulcers. However, the Arthrotec 50 formulation used in Study 349 was not the product the sponsor intends to market. The Arthrotec I formulation in this study was not demonstrated to be bioequivalent to the formulation the sponsor intends to market Product however, it was demonstrated to be bioequivalent to marketed Cytotec + Voltaren. Therefore, the efficacy information from this study can be used to support labeling for Cytotec but not for the proposed Arthrotec 50 product.

(B) *Arthrotec 75:* Arthrotec II was studied in only one of the endoscopic trials (Study 349). Study 349 patients on Arthrotec II b.i.d. had fewer gastric ulcers than did diclofenac patients; however, this difference was not statistically significant when multiple comparisons (3) were taken into account ($p=0.035$). FDA Biometrics statistical analysis found significantly fewer Arthrotec II patients with more severe lesions (i.e., 11 or more gastric erosions or ulcer) as compared to diclofenac alone patients ($p=0.004$) and concluded that Study 349 provides some support for efficacy of Arthrotec II in preventing gastric ulcers.

The Arthrotec II formulation used in this study was found to be bioequivalent to the Arthrotec 75 product the sponsor intends to market. Therefore, the results of Study 349 can be used to support approval of the proposed Arthrotec 75 product.

Based on two indirect studies, the Arthrotec 75 formulation proposed for marketing Product was not found to be bioequivalent to marketed Cytotec + Voltaren. Therefore, efficacy information from studies of Cytotec should not be directly applied to Arthrotec 75 for demonstration of efficacy in preventing ulcers.

Duodenal Ulcer:
(A) *Arthrotec 50:* Endoscopic evaluation of patients for duodenal ulcer was done in five studies. In Study 349 no significant benefit of Arthrotec I in preventing duodenal ulcers was seen. In

Studies 296, 289, and 269 where Arthrotec I and diclofenac were studied the regimen (b.i.d. or t.i.d.) was not randomized so the efficacy analyses may not be valid. An apparent benefit of Arthrotec I over diclofenac was seen in Study 289 ($p=0.008$); however, there was a statistically significant imbalance in the endoscopy rates for adverse event withdrawals between the treatment arms that may have affected the result. No apparent benefit of Arthrotec I over diclofenac alone in preventing duodenal ulcers was seen in Studies 296 or 269. In Study 321, where a randomized regimen of Arthrotec I b.i.d. was compared to naproxen and piroxicam, a statistically significant benefit over comparator NSAIDs was demonstrated ($p=0.002$ and 0.001); however, the NSAIDs used for comparison did not include diclofenac so the relevance of these comparisons to Arthrotec I versus diclofenac is not clear. In addition, the Arthrotec 50 formulation used in Study 349 was not bioequivalent to the formulation the sponsor intends to market.

Thus, no studies in this application support the effectiveness of Arthrotec I in preventing NSAID-induced duodenal ulcers.

(B) *Arthrotec 75:* Arthrotec II was studied in only one of the endoscopic trials (Study 349). In this study there was no statistically significant difference in number of patients having duodenal ulcers (including pyloric channel ulcers) in the Arthrotec II group as compared to the diclofenac alone group.

In summary, the clinical trials submitted in the Arthrotec application do not provide adequate demonstration of efficacy to support the approval of either Arthrotec 50 or Arthrotec 75. Study 349 provides some support for Arthrotec 75 b.i.d. in preventing gastric ulcers. No studies provide convincing information to support use of Arthrotec 50 or Arthrotec 75 in preventing duodenal ulcers.

Bioequivalence Approach: Arthrotec is a combination product consisting of two drugs having discrete therapeutic effects. Diclofenac exerts an anti-inflamatory effect but does not provide protection of the gastrointestinal mucosa; misoprostol provides protection of the gastrointestinal mucosa but does not exert an antiniflammatory effect. Current labeling of Cytotec (misoprostol) indicates use of the drug for prevention of NSAID-induced gastric ulcers, implying concurrent use of misoprostol and NSAID, though not specifically defining the time relationship of dosing of the drugs. Thus, there is the possibility that efficacy information for prevention of gastrointestinal ulcers for Cytotec can be used to claim efficacy for the NSAID/misoprostol combination product (i.e., Arthrotec), assuming the combination products are bioequivalent to the marketed Cytotec with regard to misoprostol and to the marketed Voltaren with regard to diclofenac sodium.

> [Using this reasoning, on a bioequivalence basis and without any clinical efficacy information using the Arthrotec formulations, Arthrotec 50, which supplies misoprostol at a dose of 200mcg/tablet could be labeled for t.i.d. use for all indications currently approved or recommended for approval for Cytotec 200mcg t.i.d., namely, for prevention of gastric ulcers in patients who are unable to tolerate Cytotec 200mcg q.i.d. (See the Division's approvable letter for Cytotec NDA 19-268/S-019 dated 6/6/96; Appendix C). With this Arthrotec 50 regimen, diclofenac would be supplied at a daily dose of 150mg which is within the approved therapeutic range for Voltaren. Four times daily dosing

(q.i.d.) would provide 800mcg of misoprostol daily and would protect againt gastric ulcer and duodenal ulcer; however, it would give a diclofenac dose of 200mg/day which is the upper limit of the dose recommended for rheumatoid arthritis. A diclofenac dose of 200mg daily is not recommended for osteoarthritis.

Arthrotec 75 could not be approved for anything purely on a bioequivalence basis because (1)a t.i.d. dose would supply diclofenac at a daily dose of 225mg, which is above the recommended daily dose for diclofenac sodium [although a diclofenac dose of 225mg/day is not specifically disallowed], and (2)misoprostol doses of less than 600mcg daily have not been approved or recommended for approval for any indication].

The sponsor has not for either of the Arhtrotec formulations proposed for marketing done a direct bioequivalency study to compare bioavailability of diclofenac and misoprostol acid from the combination products to that from marketed Voltaren and Cytotec.

Using a series of bioequivalence studies to link the various formulations, the sponsor has indirectly compared the bioavailability of the diclofenac and misoprostol* (*misoprostol acid, the active metabolite of misoprostol, was measured) in the Arthrotec formulations proposed for marketing to that of concurrently administered Cytotec (for misoprostol) and Voltaren (for diclofenac). [See Clinical Pharmacology and Biopharmaceutics Review, H-R Choi, 10/31/96]. For Arthrotec 50 a link demonstrating bioequivalence was provided between the Study 349 clinical trial formulation and marketed Cytotec + Voltaren. However, there was no clinical trial link between either the clinical trial supply or the proposed Arthrotec 50 formulation Product and already marketed Cytotec + Voltaren. Thus, at present efficacy of the misoprostol component of proposed Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg; Product cannot be established by data from use of Cytotec alone. The sponsor could perform a well-designed bioequivalence study to compare the Arthrotec 50 formulation proposed for marketing to already marketed Cytotec + Voltaren. Such a study should provide a more conclusive picture of the comparative bioavailability of the products than does the series of linked studies currently available.

For Arthrotec 75, the formulation proposed for marketing Product was not was <u>not</u> demonstrated to be bioequivalent to the Clinical Trial formulation which was shown to be bioequivalent to Cytotec + Voltaren with regard to misoprostol or diclofenac. Product C would be expected to give on average a higher diclofenac AUC and have a Cmax for diclofenac less than that of Voltaren and it would have a higher misoprostol AUC and Cmax than Cytotec alone. Thus, efficacy of proposed Arthrotec 75 cannot be asserted purely on the basis of bioequivalence to currently marketed Voltaren and Cytotec. Nevertheless, because Arthrotec would give more misoprostol than Cytotec, based on the Cytotec database for efficacy of the misoprostol component in preventing gastrointestinal ulcers, it might be reasonable to assume that q.i.d. dosing with Arthrotec 75 would be expected to prevent NSAID-induced gastric and duodenal ulcers in preventing gastric and duodenal ulcers and dosing with a t.i.d. regimen would prevent NSAID-induced gastric ulcers, in at risk patients. However, a q.i.d. regimen for Arthrotec 75 would give a daily dose of diclofenac of 300mg and a t.i.d. regimen would give 225mg; both

these diclofenac doses exceed the current labeling recommendations for Voltaren. This approach for Arthrotec 75 might be possible if Cytotec is approved at a 200mcg b.i.d. dosage for some indication.

Safety:
The safety profiles of the diclofenac/misoprostol combination products used in these clinical studies are consistent with the safety profile of approved Cytotec (misoprostol) and diclofenac sodium (Voltaren). There does not appear to be any enhanced toxicity of the combination as compared to what might be expected with concurrent usage of the individual drugs. Generally, diclofenac/misoprostol combination was well-tolerated in the clinical studies. As with diclofenac alone, abdominal pain, dyspepsia and diarrhea were the most frequent adverse events reported. Nausea was more common with treatment with diclofenac/misoprosotol than with diclofenac alone. Some patients experienced elevations in hepatic transaminases consistent with current labeling of misoprostol.

The safety concerns I have about Arthrotec relate mainly to how the drug products may be used once marketed. First, I am concerned that there may be more risk of misoprostol-related problems due to increased sharing of medication with others once misoprostol is incorporated into a "safer arthritis pill". Patients who currently understand that their NSAID treats their arthritis while their Cytotec protects the stomach may look at the combination product as an NSAID that is not as irritating to the stomach. as compared to now where it is viewed as an adjunct to the arthritis medication. Second, it is not clear how this medication will be used in the pediatric population. One argument in favor of combination products commonly is that the use of the combination entails taking fewer pills and enhances compliance. One notoriously non-compliant population is adolescent patients, and I have some concern that Arthrotec may be used in pediatric patients, such as for juvenile rheumatoid arthritis. In this regard it may be useful for the sponsor to provide information on Cytotec usage and on Arthrotec usage (European database) in pediatric patients. [Note: The sponsor has not yet proposed revised labeling for Cytotec to come into compliance with the new rule for pediatric labeling (See Federal Register, December 13, 1994, pp. 64240-64250)].

CONCLUSIONS AND RECOMMENDATIONS:
Arthrotec 50:
There are no studies in this application that can be applied to demonstrate effectiveness of the Arthrotec 50 formulation the sponsor intends to market. The product proposed for marketing was not studied in clinical trials and the products studied were not shown to be bioequivalent to the product intended for marketing. However, Study 349 does provide additional support for efficacy of misoprostol 200mcg t.i.d. alone in preventing NSAID-induced gastric ulcers, because the Study 349 formulation was found to be bioequivalent to marketed Cytotec + Voltaren.

I recommend that Arthrotec 50 not be approved for marketing at this time. The sponsor should establish bioequivalence between the Arthrotec 50 formulation proposed for marketing and marketed Cytotec + Voltaren through a direct comparison bioequivalence study. In this case, the clinical efficacy information supporting labeling of Cytotec for prevention of NSAID-induced gastric and duodenal ulcers would be applicable to Arthrotec 50.

Arthrotec 75:
The sponsor has one adequate and well-controlled clinical trial supporting effectiveness of Arthrotec 75 given b.i.d. in preventing NSAID-induced gastric ulcers and no adequate and well-controlled studies demonstrating effectiveness of Arthrotec 75 in preventing NSAID-induced duodenal ulcers. The Arthrotec 75 formulation used in the clinical trial (Study 349) was bioequivalent to the product proposed for marketing; however, the product proposed for marketing was not demonstrated to be bioequivalent to marketed Cytotec + Voltaren. Therefore, efficacy results from Cytotec studies may not be used to claim efficacy of Arthrotec 75.

I recommend that Arthrotec 75 not be approved for marketing at this time.

The sponsor should perform a bioequivalence study to directly compare the Arthrotec 75 formulation proposed for marketing to marketed Cytotec + Voltaren. If the proposed Arthrotec 75 formulation is demonstrated to be bioequivalent to Cytotec + Voltaren, the clinical efficacy information supporting labeling of Cytotec for prevention of NSAID-induced gastric and duodenal ulcers would be applicable to Arthrotec 75.

The conclusions and recommendations above may be conveyed to the sponsor.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 12/4/96

cc:
NDA 20-607
HFD-180
HFD-180/SFredd
HFD-180/KRobie-Suh
HFD-181/BStrongin
HFD-180/JChoudary
HFD-180/EDuffy
HFD-710/MFan
HFD-007/RNeuner
HFD-870/H-RChoi
f/t 12/3/96 jgw
MED\N\20607612.0KR

12/5/96
While I agree that we need bioequivalence information to use all available data re misoprostol efficacy at different doses (see November 22, 1996 letter to sponsor), with that I do not believe we will need separate efficacy studies for Arthrotec 50 and Arthrotec-75 product. These drugs release equivalent amounts of misoprostol. At the present time needed bio data is not available and therefore, recommendation seems reasonable

/S/

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DRAFT
LABELING,
DUPL. AE LETTER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	NDA 20-607 (AC)
	DEC 22 1997
Sponsor:	G. D. Searle & Co.
Drug name:	Arthrotec (diclofenac sodium/misoprostol) Tablets
Date submitted:	October 14, 1997
Date Received:	October 15, 1997
Review completed:	December 22, 1997
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
The sponsor is seeking approval of Arthrotec, a combination product consisting of diclofenac sodium as an antiinflammatory agent and misoprostol, a gastrointestinal mucosal protective agent, for treatment of arthritis in patients at high risk of developing gastrointestinal ulcers and their complications.

The NDA for Arthrotec was submitted December 22, 1995 and contained safety results from 34 clinical trials involving 8,752 patients/subjects. The current submission is a safety update which includes the data from trials which were ongoing at the time of the NDA submission or were initiated after the NDA submission and an updated summary of the worldwide post-marketing experience with Arthrotec through July 17, 1997.

Safety Information from Clinical Trials:
There were 8 trials which were ongoing at the time of the NDA submission or were initiated after the NDA submission. These trials consisted of two pharmacokinetic studies in normal subjects (Studies 359 and 360), These trials are summarized in the sponsor's table attached as Appendix A.

In the pharmacokinetic studies the most frequent adverse events reported were similar to those reported in the NDA for Phase I and Dental Pain Studies, although incidences of abdominal pain and possibly nausea and vomiting appear somewhat higher in the more recent database. The sponsor's Table 5, attached to this review as Appendix B summarizes the most frequent adverse events in these studies. None of these events was classified as serious. Six patients withdrew from these studies prematurely. Reasons for withdrawal included: anemia; rash; menstrual disorder; skin disorder; vomiting, nausea, menstrual disorder, uterine cramping; and nausea and vomiting. There were no deaths.

Study 355 is an ongoing placebo-controlled trial of Arthrotec 75 versus nabumetone and naproxen that is still blinded. Eighteen serious adverse events have been reported for this study. These include 3 gastric ulcers (1 bleeding antral ulcer, 1 perforated gastric ulcer), 1

gastritis, and one hernia. There were 4 malignancies reported: 1 malignant lymphoma of the gastric mucosa (which was felt, in retrospect, to predate study enrollment), 1 gastric carcinoid, 1 squamous cell carcinoma of the conjunctiva of the left eye, and a malignant colon polyp. Of these events, only the gastric ulcers and gastritis were felt probably related to study drug.

Studies 357 and 358, two European trials not being done under an IND, are ongoing. These trials compare efficacy and safety of Arthrotec 75 BID to meloxicam. Numbers of patients enrolled so far are not given. There have been no serious adverse events reported in Study 358 and two serious events (adenocarcinoma and arterial hypertension) in Study 357.

Three other non-IND studies have been completed and reported since the submission of the Arthrotec NDA. Most frequent adverse events among Arthrotec patients in these three studies are summarized in the following table:

Most Frequent Adverse Events among Arthrotec Patients in Studies 001, 003, and 013

Event	Study 001 (U.K.) (N=51)	Study 003 (U.K.) (N=493)	Study 013 (multinational) (N=253)
Any adverse event	70.6%	66.3%	NR
Abdominal pain	21.6%	14.6%	20.6%
Diarrhea	19.6%	14.0%	16.2%
Nausea	15.7%	7.5%	17.0%
Vomiting	11.8%	NR	NR
Headache	9.8%	NR	NR
Dyspepsia	NR	19.9%	14.2%
Flatulence	NR	5.3%	9.5%

NR = not reported

reviewer's original table, based on sponsor's text and tables

There were 2 serious adverse events in Arthrotec patients in Study 001: increased lumbar pain and fractured femur. In Study 003 there were 14 serious adverse events in Arthrotec patients, including 4 cases of previously scheduled surgery, 2 reports of cardiac failure, 2 reports of stroke (1 death), congestive heart failure and rectal hemorrhage resulting in death, bladder carcinoma resulting in death, pulmonary embolism resulting in death, esophageal carcinoma, aggravated rheumatoid arthritis, and deep vein thrombophlebitis. In Study 013 there were 15 serious adverse events in Arthrotec patients, including: 4 reports of worsening of rheumatoid arthritis leading to hospitalization, 3 reports of previously scheduled surgery, meningitis, pyelonephritis, gastroenteritis, myocardial infarction, bursitis, stroke, dyspepsia/myalgia and cholelithiasis. There were no deaths in Study 013..

The sponsor estimates that about 11 million patients have received Arthrotec worldwide. the sponsor's worldwide safety database has received 1194 post-marketing adverse event

reports. Of these, 115 were serious adverse events (42 of which were included in the NDA database). Most of the serious events involved the gastrointestinal system (77/115, 67%). Particularly, there have been more cases of serious gastrointestinal hemorrhage (21 cases in current database; up from 7 in the NDA database). The serious gastrointestinal events are displayed in the first part of sponsor's Table 9 attached to this review as Appendix C.

Reviewer's comments:
The type and frequency of adverse events in this safety update generally are similar to those of the previously existing safety database for Arthrotec. Though some adverse events are newly appearing in the spontaneous reports database, these in most cases have been reported previously with diclofenac and/or misoprostol alone. Therefore, considering the previous Arthrotec safety database and the current adverse event labeling for diclofenac sodium (Voltaren) and misoprostol (Cytotec), the current submission does not suggest the emergence of any new or unexpected safety problems with Arthrotec.

Conclusions and Recommendations:
The information in this safety update is generally consistent with the previously existing Arthrotec safety database, taking into account the current labeling for diclofenac sodium (Voltaren) and misoprostol (Cytotec). I have no new recommendations regarding the Arthrotec labeling.

APPEARS THIS WAY
ON ORIGINAL

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 12/22/97

cc:
NDA 20-607
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-181/BStrongin
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/22/97 krs
MED\N\206072212.1KR

/S/ 12-22-97

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APPENDIX A

Table 1. Arthrotec® Safety Update
List of Arthrotec® Studies ongoing at the time of NDA submission or initiated since the NDA submission

P: Protocol Number R: Report Number Short Title	Study Design*	No. of Subjects:** Mean Age: Age Range: Sex: Race:	Diagnosis	Dosage Form and Strength:	Duration of Treatment
Pharmacokinetic Studies					
P: NN2-97-02-359 R: NN2-97-08-359 Bioequivalence of Arthrotec®75 tablets	R, O, X	58 29 18/F 38/M	Healthy Adult Subjects	Arthrotec® 75 tabs Miso 200 mcg tabs Dicto 75 mg tabs Miso 200 mcg tabs + Dicto 75 mg tabs	BID administration for four days with three-day washout between treatment regimens
P: NN2-97-02-360 R: NN2-97-08-360 Bioequivalence of Arthrotec® 50 tablets	R, O, X	52 27 14/F 38/M	Healthy Adult Subjects	Arthrotec® 50 tabs Miso 200 mcg tabs Dicto 50 mg tabs Miso 200 mcg tabs + Dicto 50 mg tabs	BID administration for four days with three-day washout between treatment regimens
Phase IIIb					
P: NN2-95-02-355 R: Study ongoing Arthrotec® 75 Efficacy & UGI Safety vs. nabumetone and naproxen in OA	R, P, DB, PC, MC	Study ongoing	OA hip/knee patients with history of gastro-duodenal ulcer or ≥ 10 erosions in stomach or duodenum	Arthrotec® 75 tabs Encapsulated naproxen 500 mg tabs encapsulated nabumetone 500 mg tabs (naproxen treatment group discontinued 9/22/97) placebo tabs and capsules	Arthrotec® 75 and naproxen 500 mg BID, nabumetone 1000 mg QD, placebo BID for six weeks
Phase IV (ex-U.S.)					
P: UB8-91-02-001 R: UB8-95-08-001 Diclofenac/Misoprostol vs. Indomethacin	R, DB, MC	116 52 SWT 97/M 112 Caucasian 4 other	Patients with Ankylosing spondylitis or rheumatoid arthritis	Arthrotec® 50 tablets matching placebo tablets Indomethacin capsules matching placebo capsules	BID or TID administration 12 weeks
P: UB8-92-02-003 R: UB8-95-08-003 Arthrotec®, Diclofenac and Ibuprofen in General Practice	R, P, SB, MC	1023 66 387/F 636/M race not collected	Patients with rheumatoid arthritis or osteoarthritis	Arthrotec® 50 tablets Diclofenac 50 mg tablets Ibuprofen 800 mg tablets	BID or TID administration for four months

* O = Open, SB=Single blind, DS=Double Blind, X=Crossover, P=Parallel, R=Randomized, PC=Placebo Controlled, MC=Multicenter
** R = Randomized

Table 1. List of Arthrotec® Studies ongoing at the time of NDA submission or initiated since the NDA submission (Continued)

P: Protocol Number R: Report Number Short Title	Study Design*	No. of Subjects:** Mean Age: Age Range: Sex: Race:	Diagnosis	Dosage Form and Strength:	Duration of Treatment
P: U88-94-02-013 R: I88-96-06-013	R, SB, P, MC	514 59 35-97 161/M race not collected	Patients with rheumatoid arthritis or osteoarthritis	Arthrotec® 75 tablets diclofenac 75 mg slow release tablets	BID administration for 12 weeks
P: EN2-96-02-357 R: Study ongoing Arthrotec® 75 vs. Meloxicam Efficacy and UGI Safety in OA	R, DB, P, MC	Study ongoing	Patients with osteoarthritis	Arthrotec® 75 tablets meloxicam 15 mg tabs	Arthrotec® 75 BID or meloxicam 15 mg OD for four weeks
P: EN2-96-02-358 R: Study ongoing Arthrotec® 75 vs meloxicam NUMACT study	R, SB, X	Study ongoing	Patients with rheumatoid arthritis	Arthrotec® 75 tablets meloxicam 7.5 mg tabs meloxicam 15 mg tabs	Arthrotec® 75 BID, meloxicam 7.5 OD or meloxicam 15 mg OD for two weeks each

* O = Open, SB=Single blind, DS=Double Blind, X=Crossover, P=Parallel, R=Randomized, PC=Placebo Controlled, MC=Multicenter
** R = Randomized

APPENDIX B

Table 5. Comparison of Most Commonly Report Adverse Events from Phase I and Dental Pain Studies from Arthrotec® NDA*, Study 359 and Study 360

event	Arthrotec® ISS** (%)	Study 359 (%)	Study 360 (%)
headache	10.9	8	6
abdominal pain	7.7	12	16
menstrual disorder	6.7	0	2
nausea	6.0	10	10
uterine cramping	5.3	0	2
diarrhea	5.2	6	6
dizziness	4.7	8	6
rhinitis	4.5	6	4
coughing	1.5	4	0
dyspepsia	3.0	2	6
vomiting	1.2	2	6
pain	1.0	0	6

* Arthrotec® NDA, ISS Table 8A, Pages 103-109 of 420
** Phase I and Dental Pain Studies

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APPENDIX C

Table 9. Frequency of Serious Adverse Events in Patients Who Received Arthrotec® Reported by Body System; Ex-U.S. Phase IV Clinical Trials and Post-Marketing Experience

Gastrointestinal System Disorders	ISS*	Safety Update
Abdominal pain	0	2
Diarrhea	1	4
Nausea	2	3
Flatulence	0	1
Dyspepsia	0	1
Vomiting	0	4
GI hemorrhage	7	21
Hemorrhage rectum	1	4
Melena	0	3
Gastritis	0	2
Gastric ulcer	1	5
Hematemesis	1	2
Duodenal ulcer perforated	6	7 /
Duodenal ulcer	1	5
Gastric ulcer hemorrhagic	1	3
Duodenal ulcer hemorrhagic	1	1
Colitis	0	1
Gastric ulcer perforated	1	1
Intestinal ulceration perforated	0	1
Esophageal ulceration	1	1
Pancreatitis	0	1
Peptic ulcer	0	1
Peptic ulcer hemorrhagic	0	1
Peptic ulcer perforated	1	1
GI neoplasm benign	0	1
Body System Total	25	77
*Arthrotec® NDA, ISS, Table 36, Page 420 of 420 (1)		

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