

**P-values for Treatment Comparisons --- Study 296  
(Intent-to-Treat Cohort)**

Treatment Comparison	Final Gastric Endoscopy Scores	Final Duodenal Endoscopy Scores
With an ulcer <sup>a</sup>	0.087	0.088
With more 10 erosions or an ulcer <sup>b</sup>	0.501	0.088

P-value was obtained by Chi-square test.

<sup>a</sup> Compare patients with scores of 0-6 vs. those with scores of 7.

<sup>b</sup> Compare patients with scores of 0-4 vs. those with scores of 5-7.

Tables 19 and 20 on pages 41 and 43 in IN2-90-06-296.

Three patients in the diclofenac 50 mg/placebo group developed gastric ulcers during the four-week study period, compared with no patients in the Arthrotec 50 group. This difference, however, did not reach statistical significance.

The treatment comparison of the number of patients with a score 5 or more failed to show any significant treatment difference.

No significant treatment difference in the overall distribution of final duodenal endoscopy scores was seen.

Duodenal ulcers were found in three patients in the diclofenac 50mg/placebo group but were not observed in any patients in the Arthrotec 50 group. This difference was not statistically significant.

Four percent (4%) of the Arthrotec 50 patients had duodenal erosion or ulcers present (i.e., a score of 3 or more), compared with 7% of the diclofenac 50mg/placebo patients. However, neither this treatment difference nor the comparison of patients with a score of 5 or more was statistically significant.

The findings in endoscopy evaluable cohort of patients were similar to those described above.

The five adverse events of highest incidence in the Arthrotec 50 group were: abdominal pain, diarrhea, dyspepsia, nausea and flatulence. The incidences of all of these GI complaints were

greater in the Arthrotec 50 group than in the diclofenac 50 mg/placebo group.

### 3. Reviewer's Evaluation

#### 3.1 Review's Comments on Study Design

The study protocol did not specifically state that patient's regimen could be changed back and forth between the BID and TID; however, examination of the data from the study showed that in fact this was allowed as seen below.

Dosing	Arthrotec 50 (N=178)	Diclofenac 50 mg/placebo (N=183)
BID -	4	7
TID -	4	0
BID - BID	107	108
TID - TID	41	52
BID - TID	18	15
TID - BID	4	1

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Eighteen arthrotec patients (18, 10%) and 15 diclofenac/placebo patients (8%) had dosage regimen changed from BID to TID. Only a few patients (4 arthrotec and 1 diclofenac/placebo) had dosage regimen changed from TID to BID.

The investigator assigned the dosage regimen, either BID or TID, to control the patient's arthritis. So, patients were not assigned randomly the dosage regimen, either BID or TID.

The impact of dose changes during the study on results was not clear and needs to be investigated by the sponsor.

#### 3.2 Reviewer's Comments on Sponsor's Results on Primary Endpoint

The Chi-square test used by the sponsor may not be valid for some

of treatment comparisons (e.g., over distribution and with an ulcer) because some of the cells have expected counts less than 5. The resulting p-value would be deflated. For example, if the more appropriate method (e.g., the Fisher exact test) was used. The p-value for treatment comparison of gastric ulcer incidences would be 0.248 instead of 0.087 from the Chi-square test. So, the sponsor's results could be misleading.

#### D. OA Study NN2-94-02-349

##### 1. Description of Study

This is a multicenter (55 investigators), double-blind, placebo-controlled, randomized, parallel-group study of six weeks duration.

This study compared the incidences of gastric ulcers associated with the use diclofenac and Arthrotec 50 and Arthrotec 75 in OA patients.

Patients would be randomly assigned to receive either diclofenac 75 mg BID, Arthrotec 50 TID, Arthrotec 75 BID or placebo.

The design of study was similar to that of study 296.

The patient must demonstrate an OA flare and have a prior documented history of a gastric, pyloric channel or duodenal ulcer, or greater than ten erosions in the stomach or greater than ten erosions in the duodenum to be eligible for enrollment. However, the patient must not have an esophageal, gastric, pyloric channel or duodenal ulcer or more than ten erosions in the stomach or duodenum.

The dose regimen was determined by the randomization schedule, not by the investigator.

Each patient underwent a post-treatment endoscopy, conducted after 6 weeks in this study.

An erosion was defined the same as in RA study 289, but an ulcer was defined as any break in the mucosa with a break  $\geq 3$  mm with unequivocal depth.

The primary analyses for the assessment of gastric, duodenal and gastroduodenal mucosal damage consisted of chi-square tests comparing the outcome (ulcer, no ulcer) over the treatments. These analyses would be repeated with the outcome defined as presence or absence of mucosal damage of grade 3 or greater.

The principal pairwise comparisons were between diclofenac and Arthrotec 50 and between diclofenac and Arthrotec 75. An additional pairwise comparison would be done between Arthrotec 50 and 75 patients.

A sample size of 112 patients per treatment group is required to detect a difference between a physician's global assessment improvement rate of 70% in diclofenac, Arthrotec 50 and 75 groups and a 45% improvement rate in the placebo group with a power of 0.90 and,  $\alpha=0.0167$  (to accommodate 3 pairwise comparisons: placebo versus diclofenac, diclofenac versus Arthrotec 50, and diclofenac versus Arthrotec 75, with an experiment wise rate of 0.05), using the Cassagrande and Pike procedure which assume equal sample size in each treatment. This sample size was subsequently adjusted to take into consideration the sample size requirement for the comparison of the expected ulcer rates.

Based on previous studies it is assumed that 18% of diclofenac and 4% of Arthrotec 50 or 75 treated patient will show endoscopically confirmed gastric ulcers after six weeks of treatment. Calculations using the Cassagrande and Pike method show that a sample size of 136 patients per treatment group is required to detect this difference assuming two pairwise comparisons (diclofenac versus Arthrotec 50 and diclofenac versus Arthrotec 75), using  $\alpha=0.025$  and  $\text{power}=0.90$

Hochberg's step-down procedure will be used for planned pairwise comparisons.

## **2. Sponsor's Analysis**

Five hundred seventy-two (572) patients were randomized to receive either Arthrotec 50 TID (152 patients), Arthrotec 75 BID (175 patients), diclofenac 75 mg BID (154 patients) or placebo (91 patients).

Of the 572 patients in the Intent-to-Treat Cohort, 469 completed

the study (126 diclofenac 75 mg BID, 131 Arthrotec 50 TID, 142 Arthrotec 75 BID, and 70 placebo).

### **2.1 Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 4.

As seen from Table 4, the treatment groups were comparable in terms of age, race, gender, height, weight, affected joint, disease duration, baseline gastric and duodenal endoscopy scores, physician's or patient's global assessments, baseline OA severity index, and functional capacity classification.

### **2.2 Sponsor's Analysis of Endoscopy Data**

Five hundred nineteen (519) patients (138 diclofenac 75 mg BID, 142 Arthrotec 50 TID, 159 Arthrotec 75 BID, and 80 placebo) underwent a final endoscopy and are included in the Intent-to-Treat cohort endoscopy analyses.

Four hundred fifty-two (452) patients (122 diclofenac 75 mg BID, 129 Arthrotec 50 TID, 134 Arthrotec 75 BID, and 67 placebo) were evaluable for endoscopic analyses.

The distribution of final gastric endoscopy scores in the four treatment groups is given below.

#### **2.2.1 Final Gastric Endoscopy Scores**

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**Final Gastric Endoscopy Scores --- Study 349  
(Intent-to-Treat Cohort)**

**Number of Patients (%)**

Score	Diclofenac 75 mg BID (N=138)	Arthrotec 50 TID (N=142)	Arthrotec 75 BID (N=159)	Placebo (N=80)
0	60 (43%)	91 (64%)	103 (65%)	57 (71%)
1	12 (9%)	18 (13%)	15 (9%)	4 (5%)
2	7 (5%)	7 (5%)	9 (6%)	2 (3%)
3	32 (23%)	18 (13%)	22 (14%)	10 (13%)
4	8 (6%)	1 (1%)	3 (2%)	3 (4%)
5	4 (3%)	3 (2%)	0 (0%)	2 (3%)
6	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	15 (11%)	4 (3%)	7 (4%)	2 (3%)

Table 17 on page 74 in IN2-95-06-349

**P-values for Treatment Comparisons --- Study 349  
(Intent-to-Treat Cohort)**

Treatment Comparison	Diclofenac 75 mg BID vs. Arthrotec 50 TID	Diclofenac 75 mg BID vs. Arthrotec 75 BID	Arthrotec 50 TID vs. Arthrotec 75 BID
With an ulcer <sup>a</sup>	0.007*	0.034	0.464
With more 10 erosions or an ulcer <sup>b</sup>	0.011*	0.004*	0.828

P-value was obtained by Chi-square test.

<sup>a</sup> Compare patients with scores of 0-6 vs. those with scores of 7.

<sup>b</sup> Compare patients with scores of 0-4 vs. those with scores of 5-7.

\* Statistically significant at the 5% level for primary pairwise comparison using Hochberg's step-down procedure.

Pairwise treatment comparisons revealed statistically significant differences in gastric ulcer incidence when diclofenac 75 mg BID was compared with Arthrotec 50 TID..

### 2.2.2 Final Duodenal Endoscopy Scores

The distribution of final duodenal endoscopy scores in the four treatment groups is given below.

**Final Duodenal Endoscopy Scores --- Study 349  
(Intent-to-Treat Cohort)**

**Number of Patients (%)**

Score	Diclofenac 75 mg BID (N=138)	Arthrotec 50 TID (N=142)	Arthrotec 75 BID (N=159)	Placebo (N=80)
0	102 (74%)	119 (84%)	133 (84%)	63 (79%)
1	9 (7%)	8 (6%)	9 (6%)	4 (5%)
2	2 (1%)	0 (0%)	2 (1%)	1 (1%)
3	15 (11%)	5 (4%)	10 (6%)	11 (14%)
4	1 (1%)	1 (1%)	1 (1%)	0 (0%)
5	0 (0%)	1 (1%)	0 (0%)	0 (0%)
6	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	9 (7%)	8 (6%)	4 (3%)	1 (1%)

Table 18 on page 76 in IN2-95-06-349

**P-values for Treatment Comparisons --- Study 349  
(Intent-to-Treat Cohort)**

Treatment Comparison	Diclofenac 75 mg BID vs. Arthrotec 50 TID	Diclofenac 75 mg BID vs. Arthrotec 75 BID	Arthrotec 50 TID vs. Arthrotec 75 BID
With an ulcer <sup>a</sup>	0.756	0.092	0.167
With more 10 erosions or an ulcer <sup>b</sup>	0.950	0.092	0.103

P-value was obtained by Chi-square test.

<sup>a</sup> Compare patients with scores of 0-6 vs. those with scores of 7.

<sup>b</sup> Compare patients with scores of 0-4 vs. those with scores of 5-7.

\* Statistically significant at the 5% level for primary pairwise comparison using Hochberg's step-down procedure.

Pairwise treatment comparisons demonstrated no statistically significant differences in the incidence of duodenal ulcers between the diclofenac 75 mg BID group and the Arthrotec 50 TID

or Arthrotec 75 BID groups.

No statistically significant differences were found between Arthrotec 50 TID and Arthrotec 75 BID in any of the endoscopic analyses.

Analyses of results of the Endoscopy Evaluable cohort showed differences similar to those described above.

The five events of highest incidence in the Arthrotec 50 TID and Arthrotec 75 BID groups were dyspepsia, abdominal pain, diarrhea, and nausea.

Sixty-three (63) patients withdrew from study due to adverse events: 20 diclofenac 75 mg BID patients (13%), 104 Arthrotec 50 TID patients (9%), 23 Arthrotec 75 BID patients (13%), and six placebo patients (7%).

### **3. Reviewer's Evaluation**

This study was well-controlled and conducted. The dose regimen was determined by the randomization schedule, not by the investigator.

Pairwise treatment comparisons demonstrated no statistically significant differences in incidence of gastric ulcers between the Arthrotec 75 BID group and diclofenac 75 mg BID group ( $p=0.034$ ) after adjusting for multiple comparisons by the Hochberg's procedure. However, the proportions of patients with 11 or more gastric erosions or ulcer (score of 5 or more) were significantly lower in the Arthrotec 75 BID than in the diclofenac 75 mg BID group ( $p=0.004$ ).

So, study 349 provides some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

## **E. IN2-90-02-321**

### **1. Description of Study**

The study was a multicenter (71 investigators), double-blind, randomized, active-controlled, parallel-group trial.

The primary objective of this study was to compare the gastroduodenal damage associated with the use of Arthrotec 50 with that associated with piroxicam 10 mg BID or naproxen 375 mg BID when administered to patients with osteoarthritis for four weeks.

The design of this study was similar to that of Study 296. But dose regimen was fixed and would be not changed by the investigator.

Patients must have been diagnosed as having had osteoarthritis of the hip and/or knee for at least three-months, with a functional capacity classification of I-III.

Each patient underwent a post-treatment endoscopy, conducted after 4 weeks in this study.

The primary analysis for the assessment of mucosal damage would consist of log-linear analysis, with investigator, treatment and outcome (presence or absence of ulceration) and their interactions-as factors, to test for statistically significant treatment interactions. The analysis would be repeated with the outcome defined as presence or absence of mucosal damage of grade 5 or greater. In addition, the distribution of patients by final endoscopic grade would be compared for the three treatment groups using the Kruskal-Wallis test.

The sample size of 200 patients per treatment group (600 patients in all) was chosen on the basis of clinical judgement. Assuming that approximately 15% of either the piroxicam or naproxen treated groups develop ulcers during the study, the sample size would be sufficient to detect a treatment difference, with a power of at least 0.9 (using two-sided tests of significance at the 5% level), if Arthrotec ulcer incidence rate was 3.8% or less. This ulcer incidence permitted three pairwise treatment comparisons at the combined 5% significance level using the Bonferroni approach.

## **2. Sponsor's Analysis**

Six hundred and forty-four (644) patients were randomly assigned to receive either Arthrotec 50 BID (216 patients), piroxicam 10 mg BID (218 patients), or naproxen 375 mg BID (210 patients).

Data on one piroxicam patient was lost and remains unavailable for efficacy analysis.

Of the 643 patients in the Intent-to-Treat cohort, 578 completed the study (193, Arthrotec; 200, piroxicam; 185, naproxen). A total of 65 patients withdrew before completion (23, Arthrotec; 17, piroxicam; 25, naproxen). A total of 48 patients withdrew from study due to adverse events (18, Arthrotec; 10, piroxicam; 20, naproxen).

### **2.1 Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 5.

As seen from Table 5, the treatment groups were comparable in terms of height, weight, baseline gastric and duodenal endoscopy scores, baseline assessments of osteoarthritis status (Physician's and Patient's Global Assessment, Functional Capacity, and Patient's Assessment of Joint Pain).

A statistically significant treatment group difference was noted in the baseline Osteoarthritis Severity Index ( $p=0.024$ ). The mean Osteoarthritis Severity Index for patients randomized to Arthrotec was 11.93. The mean index was 11.00 for the piroxicam group and 11.51 for the naproxen group. This difference was not considered medically meaningful.

Baseline endoscopy scores of the gastric mucosa showed a significantly different distribution between U.S. and ex-U.S. patients, with a higher percentage of U.S. patients having a normal gastric mucosa (83%) at the baseline compared to ex-U.S. patients (62%).

### **2.2 Sponsor's Analysis of Endoscopy Data**

Forty-one (41) patients (16, Arthrotec; 13, piroxicam; 12, naproxen) did not have a final endoscopy performed. These patients were not included in the Intent-to-Treat cohort analysis.

Four hundred and seventy-nine (479) patients (158, Arthrotec; 164, piroxicam; 157, naproxen) were judged to be evaluable for

endoscopic assessments.

Chi-square tests were used to compare final gastroduodenal, gastric and duodenal endoscopy scores and changes from pre- to posttreatment endoscopy scores.

### 2.2.1 Final Gastric Endoscopy Scores

The distribution of final gastric endoscopy scores in the three treatment groups is given below.

#### Final Gastric Endoscopy Scores --- Study 321 (Intent-to-Treat Cohort)

Number of Patients (%)

Score	Arthrotec 50 BID (N=200)	Piroxicam 10 mg BID (N=204)	Naproxen 375 mg BID (N=198)
0	156 (78%)	112 (55%)	73 (37%)
1	14 (7%)	13 (6%)	17 (9%)
2	4 (2%)	4 (2%)	4 (2%)
3	19 (10%)	48 (24%)	56 (28%)
4	4 (2%)	10 (5%)	17 (9%)
5	0 (0%)	3 (1%)	15 (8%)
6	0 (0%)	0 (0%)	1 (1%)
7	3 (2%)	14 (7%)	15 (8%)

Table 17 on page 50 in IN2-92-06-321

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**P-values for Treatment Comparisons --- Study 321  
(Intent-to-Treat Cohort)**

Treatment Comparison	Arthrotec 50 BID vs. Piroxicam 10 mg BID	Arthrotec 50 BID vs. Naproxen 375 mg BID	Piroxicam 10 mg BID vs. Naproxen 375 mg BID
With an ulcer <sup>a</sup>	0.007*	0.004*	0.782
With more 10 erosions or an ulcer <sup>b</sup>	0.002*	0.000*	0.024

P-value was obtained by Chi-square test.

<sup>a</sup> Compare patients with scores of 0-6 vs. those with scores of 7.

<sup>b</sup> Compare patients with scores of 0-4 vs. those with scores of 5-7.

\* Statistically significant at the 1.7% level (pairwise comparisons)

Fourteen (14) patients (7%) in the piroxicam group and 15 patients (8%) in the naproxen group developed gastric ulcers during the four-week study period, compared with three patients (2%) in the Arthrotec group. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences between Arthrotec and piroxicam, Arthrotec and naproxen, but not between piroxicam and naproxen.

Seventeen (17) patients (8%) in the piroxicam group and 31 patients (16%) in the naproxen group showed clinically significant gastric lesions including ulcers (i.e., a score of 5 or more) compared with three patients (2%) in the Arthrotec group. Pairwise treatment comparisons of these gastric lesions reached statistical significance in favor of Arthrotec versus piroxicam and naproxen.

### 2.2.2 Final Duodenal Endoscopy Scores

The distribution of final duodenal endoscopy scores in the three treatment groups is given below.

**Final Duodenal Endoscopy Scores --- Study 321  
(Intent-to-Treat Cohort)**

**Number of Patients (%)**

Score	Arthrotec 50 BID (N=200)	Piroxicam 10 mg BID (N=204)	Naproxen 375 mg BID (N=198)
0	181 (91%)	173 (85%)	159 (80%)
1	6 (3%)	3 (1%)	7 (4%)
2	1 (1%)	0 (0%)	0 (0%)
3	8 (4%)	14 (7%)	20 (10%)
4	4 (2%)	3 (1%)	6 (3%)
5	0 (0%)	1 (1%)	3 (2%)
6	0 (0%)	0 (0%)	0 (0%)
7	0 (0%)	10 (5%)	3 (2%)

Table 18 on page 52 in IN2-92-06-321

**P-values for Treatment Comparisons --- Study 321  
(Intent-to-Treat Cohort)**

Treatment Comparison	Arthrotec 50 BID vs. Piroxicam 10 mg BID	Arthrotec 50 BID vs. Naproxen 375 mg BID	Piroxicam 10 mg BID vs. Naproxen 375 mg BID
With an ulcer <sup>a</sup>	0.002*	0.081	0.055
With more 10 erosions or an ulcer <sup>b</sup>	0.001*	0.013*	0.239

Table 18 on page 52 in IN2-92-06-321

P-value was obtained by Chi-square test.

<sup>a</sup> Compare patients with scores of 0-6 vs. those with scores of 7.

<sup>b</sup> Compare patients with scores of 0-4 vs. those with scores of 5-7.

\* Statistically significant at the 1.7% level (pairwise comparisons).

Duodenal ulcers were observed in 10 patients (5%) in the piroxicam group and three patients (2%) in the naproxen group but were not observed in any patients in the Arthrotec group. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences only between Arthrotec and piroxicam. Comparisons between Arthrotec and naproxen failed to reach statistical significance.

Eleven (11) patients (5%) in the piroxicam group and six (3%) in the naproxen group had clinically significant duodenal lesions including ulcer (i.e., a score of 5 or more), while no patients receiving Arthrotec experienced such damage. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences between Arthrotec and piroxicam, Arthrotec and naproxen, but not between piroxicam and naproxen.

### **3. Reviewer's Evaluation**

The diclofenac 50 mg BID was not included in this study. The superiority of Arthrotec 50 BID over either piroxicam 10 mg BID or naproxen 375 mg BID does not imply the superiority of Arthrotec 50 BID over diclofenac 50 mg BID.

### **F. Overall Summary and Recommendation**

#### **1. Prevention of Developing NSAID-induced Gastric Ulcer**

##### **Arthrotec 50 BID-TID (protocols 296 and 289)**

In an OA study (protocol 296), after four weeks of treatment with Arthrotec 50 BID-TID or diclofenac 50 mg BID-TID, no significant differences were observed between treatment groups in terms of the number of patients with gastric ulcer.

In the second, a RA study (protocol 289), after 12 weeks of treatment with the same dosing regimens, no significant differences were observed between treatment groups in terms of the number of patients with gastric ulcer.

Both studies 296 and 289 failed to provide support of the efficacy of Arthrotec 50 BID-TID for prevention of developing NSAID-induced gastric ulcers. The p-value for the primary efficacy endpoint according to the sponsor's analysis was 0.641 for study 289 and 0.087 for study 296.

##### **Arthrotec 50 BID (protocol 321)**

In the four-week, active-controlled OA trial (protocol 321) comparing Arthrotec 50 BID with piroxicam 10 mg BID and naproxen 375 mg BID, pairwise treatment comparisons of gastric ulcers reached statistically significance in favor of Arthrotec 50 BID

versus piroxicam 10 mg BID and naproxen 375 mg BID.

Study 321 provides support of the efficacy of the Arthrotec 50 BID against piroxicam 10 mg BID and naproxen 375 BID for prevention of developing NSAID-induced gastric ulcers. However, superiority of Arthrotec 50 BID to diclofenac 50 mg BID has not been demonstrated in this trial.

#### **Arthrotec 50 TID (protocol 349)**

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, the proportions of patients with gastric ulcers were significantly lower in the Arthrotec 50 TID than in the diclofenac 75 mg BID.

Study 349 provides support of the efficacy of the Arthrotec 50 TID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

#### **Arthrotec 75 BID (protocol 349)**

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of gastric ulcers between the Arthrotec 75 BID and diclofenac 75 mg BID group after adjusting for multiple comparisons by the Hochberg's procedure.

However, the proportions of patients with 11 or more gastric erosions or ulcer (score of 5 or more) were significantly lower in the Arthrotec 75 BID than in the diclofenac 75 mg BID group.

Study 349 provides some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

## **2. Prevention of Developing NSAID-induced Duodenal Ulcer**

#### **Arthrotec 50 BID-TID (protocols 296 and 289)**

In an OA study (protocol 296), after four weeks of treatment with

Arthrotec 50 BID-TID or diclofenac 50 mg BID-TID, no significant differences were observed between treatment groups in terms of the number of patients with ulcer for duodenal ulcers.

In the second, a RA study (protocol 289), after 12 weeks of treatment with the same dosing regimens, it was observed that statistically significantly fewer endoscoped Arthrotec 50 patients had duodenal ulcer (score=7) as compared to diclofenac 50 mg/placebo. However, this significant result was doubtful due to the fact of a large discrepancy between treatment groups in the proportion of adverse event withdrawals having final endoscopy (56% of diclofenac/placebo; 15% of Arthrotec). This might compromise the statistical analysis of the between treatment group difference in duodenal ulcer rate.

Study 296 failed to provide support of the efficacy of Arthrotec 50 BID-TID. Study 289 provides some support of the efficacy of Arthrotec 50 BID-TID against diclofenac 50 mg BID-TID in terms of prevention of developing NASID-induced duodenal ulcer. However, the results are not replicated in study 296. The superiority might be due to the discrepancy between treatment groups in the proportion of adverse event withdrawals having final endoscopy.

#### **Arthrotec 50 BID (protocol 321)**

In the four-week, active-controlled OA trial (protocol 321) comparing Arthrotec 50 BID with piroxicam 10 mg BID and naproxen 375 mg BID, pairwise treatment comparisons of duodenal ulcers demonstrated statistically significant difference only between Arthrotec 50 BID and piroxicam 10 mg BID. Comparisons between Arthrotec 50 BID and naproxen 375 mg BID failed to reach statistical significance.

Study 321 provides support of the efficacy of the Arthrotec 50 BID against piroxicam 10 mg BID for prevention of developing NSAID-induced duodenal ulcers. However, superiority of Arthrotec 50 BID to diclofenac 50 mg BID has not been demonstrated in this trial.

#### **Arthrotec 50 TID (protocol 349)**

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or

erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of duodenal ulcers between the Arthrotec 50 TID and diclofenac 75 mg BID group.

Study 349 failed to support of the efficacy of the Arthrotec 50 TID against diclofenac 75 mg BID for prevention of developing NSAID-induced duodenal ulcer.

**Arthrotec 75 BID (protocol 349)**

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of duodenal ulcers between the Arthrotec 75 BID and diclofenac 75 mg BID group.

Study 349 failed to support of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced duodenal ulcer.

**G. Comments to be conveyed to the Sponsor**

The contents of Section F may be conveyed to the sponsor.

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Milton C. Fan, Ph.D.  
Mathematical Statistician

This review consists of 29 pages of text and 5 pages of tables.

concur: Dr. Huque  
Dr. Smith

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cc:  
Archival NDA 20-607

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HFD-180  
HFD-180/Dr. Fredd  
HFD-180/Dr. Robie-Suh  
HFD-180/Mr. Strongin  
HFD-344/Dr. Lisook  
HFD-720

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HFD-720/Chron.  
HFD-720/Dr. Smith  
HFD-720/Dr. Huque  
HFD-720/Dr. Fan  
Dr. Fan/x73088/mcf/09/09/96

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Table 1 Comparability of Treatment Groups --- Protocol 289

		Intent-to-Treat Population		
Variable	Level	Diclofenac/ Misoprostol	Diclofenac/ Placebo	between treatment p-value
		50 mg/200 mcg BID-TID (n=164)	50 mg/0 mcg BID-TID (n=175)	
Sex	Male	41 (25%)	38 (22%)	0.475
	Female	123 (75%)	137 (78%)	
Age (mean)		53.2	53.4	0.843
Height (cm) (mean)		162.6	162.5	0.608
Weight (kg) (mean)		66.2	65.2	0.568
Race	Caucasian	130 (79%)	148 (85%)	0.132
	Black	10 (6%)	3 (2%)	
	Oriental	1 (1%)	0 (0%)	
	Other	23 (14%)	24 (14%)	
Disease Duration	<0.5 (years)	3 (2%)	4 (2%)	0.285
	0.5 - 0.9	5 (3%)	6 (3%)	
	1.0 - 4.9	40 (24%)	52 (30%)	
	5.0 - 9.9	45 (27%)	48 (27%)	
	10.0 - 14.9	45 (27%)	34 (19%)	
	> 15.0	26 (16%)	31 (18%)	
Endoscopy Scores Gastric	0	107 (65%)	112 (64%)	0.463
	I	10 (6%)	16 (9%)	
	2	3 (2%)	2 (1%)	
	3	29 (18%)	36 (21%)	
	4	15 (9%)	9 (5%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	
unknown	0 (0%)	0 (0%)		
Endoscopy Scores Duodenal	0	150 (91%)	149 (85%)	0.347
	1	2 (1%)	5 (3%)	
	2	0 (0%)	1 (1%)	
	3	9 (5%)	17 (10%)	
	4	3 (2%)	2 (1%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	
unknown	0 (0%)	1 (1%)		
Physician's global assessment	Very good	5 (3%)	3 (2%)	0.802
	Good	55 (34%)	51 (29%)	
	Fair	70 (43%)	83 (47%)	
	Poor	32 (20%)	36 (21%)	
	Very Poor	2 (1%)	2 (1%)	
Patient's global assessment	Very good	5 (3%)	3 (2%)	0.678
	Good	48 (29%)	52 (30%)	
	Fair	75 (46%)	77 (44%)	
	Poor	32 (20%)	34 (19%)	
	Very Poor	4 (2%)	9 (5%)	
Functional Capacity	I	18 (11%)	17 (10%)	0.752
	II	110 (67%)	123 (70%)	
	III	34 (21%)	31 (18%)	
	IV	2 (1%)	4 (2%)	

Compiled from Tables 10-13, pages 31-35, IN2-90-06-289.  
P-values for age, height, weight, and disease duration were obtained using  
Mann-Whitney nonparametric test.  
P-values for other variables were obtained using Pearson's chi-square test.

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Table 3 Comparability of Treatment Groups --- Protocol 296

		Intent-to-Treat Population		
Variable	Level	Diclofenac/ Misoprostol	Diclofenac/ Placebo	between treatment p-value
		50 mg/200 mcg BID-TID (n=178)	50 mg/0 mcg BID-TID (n=183)	
Sex	Male	43 (24%)	54 (30%)	0.252
	Female	135 (76%)	129 (70%)	
Age (mean)		59.2	61.3	0.110
Height (cm) (mean)		160.5	161.7	0.342
Weight (kg) (mean)		70.4	73.8	0.004
Race	Caucasian	158 (89%)	160 (87%)	0.785
	Black	5 (3%)	5 (3%)	
	Oriental	0 (0%)	1 (1%)	
	Other	15 (8%)	17 (9%)	
Disease Duration	<0.5 (years)	0 (0%)	4 (2%)	0.514
	0.5 - 0.9	7 (4%)	7 (4%)	
	1.0 - 4.9	68 (38%)	67 (37%)	
	5.0 - 9.9	51 (29%)	42 (23%)	
	10.0 - 14.9	30 (17%)	36 (20%)	
	> 15.0	22 (12%)	27 (15%)	
Endoscopy Scores Gastric	0	121 (68%)	123 (67%)	0.600
	1	18 (10%)	22 (12%)	
	2	0 (0%)	3 (2%)	
	3	25 (14%)	24 (13%)	
	4	11 (6%)	9 (5%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	1 (1%)	0 (0%)	
	unknown	2 (1%)	2 (1%)	
Endoscopy Scores Duodenal	0	155 (87%)	153 (84%)	0.375
	1	12 (7%)	14 (8%)	
	2	0 (0%)	0 (0%)	
	3	6 (3%)	13 (7%)	
	4	2 (1%)	1 (1%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	2 (1%)	0 (0%)	
	unknown	1 (1%)	2 (1%)	
Physician's global assessment	Very good	2 (1%)	1 (1%)	0.981
	Good	36 (20%)	39 (21%)	
	Fair	103 (58%)	105 (57%)	
	Poor	36 (20%)	37 (20%)	
	Very Poor	1 (1%)	1 (1%)	
Patient's global assessment	Very good	2 (1%)	4 (2%)	0.802
	Good	27 (15%)	33 (18%)	
	Fair	94 (53%)	97 (53%)	
	Poor	49 (28%)	43 (23%)	
	Very Poor	6 (3%)	6 (3%)	
Functional Capacity	I	22 (12%)	17 (9%)	0.583
	II	128 (72%)	133 (73%)	
	III	28 (16%)	33 (18%)	
	IV	0 (0%)	0 (0%)	
OA severity index (mean)		11.15	11.20	0.783

Compiled from Tables 13-16, pages 32-37, IN2-90-06-296.  
P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Mann-Whitney nonparametric test.  
P-values for other variables were obtained using Pearson's chi-square test.

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Table 2 Reanalysis of Duodenal Ulcer Occurrence with Arthrotec 50 as Compared to Diclofenac 50 mg/Placebo --- Study 289

Analysis	Diclofenac/Placebo (n = 175)	Diclofenac/Misoprostol (n = 164)	P-Value*
Equal probability imputation using LOCF <sup>b</sup> for all patients except for "unknown" adverse event withdrawals for whom the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo	16/175	9/164	0.218
Equal probability imputation excluding "unknown" except for "unknown" adverse event withdrawals for whom the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo	16/162	9/156	0.213
Equal probability imputation using placebo incidence rate (8%) for both "unknown" misoprostol and "unknown" placebo patients who were not adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	17/175	10/164	0.235
Equal probability imputation using misoprostol incidence rate (1%) for both "unknown" misoprostol and "unknown" placebo patients who were <del>not</del> adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	16/175	9/164	0.218
Equal probability imputation using misoprostol incidence rate (1%) for "unknown" placebo patients who were not adverse event withdrawals and placebo incidence rate (8%) for "unknown" misoprostol patients who were not adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	16/175	10/164	0.315

- \* "unknown" refers to missing (not done) final endoscopy
- \* p-value = 2-sided p-value determined by Fisher's exact test (M. Fan, FDA Biometrics)
- \* LOCF = last observation carried forward
- \* pyloric channel ulcers (2 diclofenac/placebo and 1 diclofenac/misoprostol) are counted with the duodenal ulcers.

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Table 4 Comparability of Treatment Groups --- Protocol 3

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## Intent-to-Treat Population

Variable	Level	Diclofenac 75 mg BID (n=154)	Arthrotec 50 mg TID (n=152)	Arthrotec 50 mg BID (n=175)	Placebo (n=91)	between treatment p-value
Sex	Male	44 (29%)	49 (32%)	58 (33%)	29 (32%)	0.831
	Female	110 (71%)	103 (69%)	117 (67%)	62 (68%)	
Age (mean)		62.9	62.3	62.8	61.5	0.505
Height (cm) (mean)		167.5	167.0	166.8	167.5	0.868
Weight (kg) (mean)		88.9	87.4	84.7	89.1	0.276
Race	Caucasian	127 (92%)	134 (89%)	151 (86%)	79 (87%)	0.814
	Black	21 (14%)	14 (9%)	17 (10%)	10 (11%)	
	Oriental	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	6 (4%)	4 (3%)	7 (4%)	2 (2%)	
Disease Duration (yrs) (mean)		11.9	11.9	10.3	10.6	0.389
Endoscopy Scores	0	98 (64%)	103 (68%)	120 (69%)	64 (70%)	0.938
	1	11 (7%)	11 (7%)	13 (7%)	6 (7%)	
	2	6 (4%)	7 (5%)	4 (2%)	3 (3%)	
	3	33 (21%)	23 (15%)	33 (19%)	16 (18%)	
	4	6 (4%)	8 (5%)	5 (3%)	2 (2%)	
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Endoscopy Scores Duodenal	0	135 (88%)	134 (88%)	153 (87%)	76 (84%)	0.625
	1	6 (4%)	7 (5%)	7 (4%)	3 (3%)	
	2	1 (1%)	1 (1%)	3 (2%)	2 (2%)	
	3	12 (8%)	9 (6%)	9 (5%)	10 (11%)	
	4	0 (0%)	1 (1%)	3 (2%)	0 (0%)	
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Physician's global assessment	Very good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.092
	Good	3 (2%)	2 (1%)	8 (5%)	1 (1%)	
	Fair	30 (19%)	26 (17%)	36 (21%)	14 (15%)	
	Poor	107 (69%)	119 (78%)	120 (69%)	74 (81%)	
	Very Poor	14 (9%)	5 (3%)	11 (6%)	2 (2%)	
Patient's global assessment	Very good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.093
	Good	4 (3%)	3 (2%)	6 (3%)	1 (1%)	
	Fair	26 (17%)	30 (20%)	24 (14%)	22 (24%)	
	Poor	92 (60%)	103 (68%)	123 (70%)	59 (65%)	
	Very Poor	32 (21%)	16 (11%)	22 (13%)	9 (10%)	
Functional Capacity	I	6 (4%)	4 (3%)	11 (6%)	4 (4%)	0.449
	II	124 (81%)	126 (83%)	145 (83%)	70 (77%)	
	III	24 (16%)	22 (14%)	19 (11%)	17 (19%)	
	IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
OA severity index (mean)		14.2	14.0	14.0	13.9	0.898

Compiled from Tables 11-15, pages 63-69, IN2-95-06-349.

P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Kruskal-Wallis nonparametric test.

P-values for other variables were obtained using Pearson's chi-square test.

Table 5 Comparability of Treatment Groups --- Protocol 321

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		Intent-to-Treat Population			
Variable	Level	Diclofenac/ Misoprostol	Piroxicam	Naproxen	between treatment p-value
		50 mg/200 mcg BID (n=216)	10 mg BID (n=217)	375 mg BID (n=210)	
Sex	Male	52 (24%)	55 (25%)	48 (23%)	0.835
	Female	164 (76%)	162 (75%)	162 (77%)	
Age (mean)		60.7	58.7	59.5	0.117
Height (cm) (mean)		161.4	161.8	162.6	0.898
Weight (kg) (mean)		77.5	76.3	77.2	0.294
Race	Caucasian	177 (82%)	172 (79%)	169 (80%)	0.982
	Black	17 (8%)	21 (10%)	20 (10%)	
	Oriental	1 (0%)	2 (1%)	1 (0%)	
	Other	21 (10%)	22 (10%)	20 (10%)	
Disease Duration (years)	<0.5	4 (2%)	6 (3%)	1 (0%)	0.395
	0.5 - 0.9	9 (4%)	10 (5%)	9 (4%)	
	1.0 - 4.9	72 (33%)	94 (43%)	79 (38%)	
	5.0 - 9.9	69 (32%)	44 (20%)	59 (28%)	
	10.0 - 14.9	39 (18%)	33 (15%)	30 (14%)	
	>15.0	23 (11%)	30 (14%)	32 (15%)	
Endoscopy Scores Gastric	0	145 (67%)	141 (65%)	146 (70%)	0.847
	1	12 (6%)	16 (7%)	11 (5%)	
	2	3 (1%)	2 (1%)	3 (1%)	
	3	31 (14%)	34 (16%)	23 (11%)	
	4	25 (12%)	24 (11%)	26 (12%)	
	5	0 (0%)	0 (0%)	1 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	
unknown	0 (0%)	0 (0%)	0 (0%)		
Endoscopy Scores Duodenal	0	202 (94%)	191 (88%)	195 (93%)	0.318
	1	4 (2%)	8 (4%)	6 (3%)	
	2	0 (0%)	0 (0%)	0 (0%)	
	3	5 (2%)	12 (6%)	4 (2%)	
	4	5 (2%)	6 (3%)	5 (2%)	
	5	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	
unknown	0 (0%)	0 (0%)	0 (0%)		
Physician's global assessment	Very good	0 (0%)	1 (0%)	0 (0%)	0.284
	Good	3 (1%)	4 (2%)	2 (1%)	
	Fair	126 (58%)	148 (68%)	135 (65%)	
	Poor	75 (35%)	50 (23%)	58 (28%)	
	Very Poor	12 (6%)	14 (7%)	14 (7%)	
Patient's global assessment	Very good	0 (0%)	1 (0%)	0 (0%)	0.377
	Good	3 (1%)	3 (1%)	2 (1%)	
	Fair	107 (50%)	129 (59%)	122 (58%)	
	Poor	85 (39%)	62 (29%)	66 (32%)	
	Very Poor	21 (10%)	22 (10%)	19 (9%)	
Functional Capacity	I	18 (8%)	35 (16%)	21 (10%)	0.059
	II	165 (76%)	160 (74%)	164 (78%)	
	III	33 (15%)	22 (10%)	24 (11%)	
	IV	0 (0%)	0 (0%)	0 (0%)	
OA severity index (mean)		11.93	11.00	11.51	0.024

Compiled from Tables 12-15, pages 42-45, IN2-92-06-321.

P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Kruskal-Wallis nonparametric test.

P-values for other variables were obtained using Pearson's chi-square test.

Statistical Review and Evaluation -- Stability

Date: OCT 21 1996

NDA #: 20-607

Applicant: G. D. Searle & Company

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

Documents Reviewed: Original Amendment Dated February 23, 1996  
Amendment Dated March 8, 1996

**A. Background**

In this NDA submission, the sponsor has submitted 12 months stability data for Arthrotec and has requested a 36 month expiration dating period for this drug product. Dr. George Chen, reviewing chemist in HFD-180, has requested a statistical review and evaluation of the sponsor's stability data analyses.

The sponsor performed the analysis of 25 °C assay and degradation product data from the primary stability studies for diclofenac sodium/misoprostol drug product. Included for stability analysis are bottles and paper/foil/foil/paper strips for two different strength tablets: 50 mg diclofenac sodium/200 mcg misoprostol (50/200) and 75 mg diclofenac sodium/200 mcg misoprostol (75/200).

This review will only address on potency data in the 25°C storage.

**B. Sponsor's Results**

All lots have been on stability for 52 weeks except for lots 480110, 480100, and 480090 which have been on stability for 104 weeks.

Values for assay and for the degradation products are reported as percent of label claim. All values for the degradation products reported at their limit of quantitation of <0.5% were set to 0.25% for calculations.

The sponsor used the FDA SAS DRUG Formulation Stability Program

(3/09/92) to generate the results of the estimated dating period in months for all the lots in the various package types.

The program performs the expiration dating period estimation based on linear regression analysis. For each package type, each set of three lots was submitted into the program to initially test for equalities of intercepts and/or slopes.

Based on a full-vs-reduced model approach, pooling of intercepts and/or slopes was performed where appropriate. For each fit, the standard errors of the mean predicted values were used to generate a one-sided 95% lower confidence bound for assay and a one-sided 95% upper confidence bound for degradation products. For both diclofenac sodium and misoprostol assay, the lower specification limits of 90% was used to estimate expiry. For SC-29636, SC-32759 and SC-33188, the respective upper specification limits of 3.5%, 2.0% and 0.7% were used to estimate expiry.

The resulting estimated dating periods in months for all the lots in the various package types are summarized in Table 1.

### C. Reviewer's Results

This reviewer ran the Division's routine stability program and had verified the sponsor's estimated dating periods for all the lots in three package types for 50/200 and 75/200 strength for diclofenac sodium, misoprostol, and SC-29636.

With respect to all five quantities:

Diclofenac Sodium	90%-110%
Misoprostol	90%-110%
SC-29636	≥3.5%
SC-32759	≥2.0%
SC-33188	≥0.7%

expiration dating periods for all the lots in the various package types are:

Strength	Lot No.	Est. Expiration Dating Period (Months)	
50/200	653310	48	
	653320	48	
	664680	35	
	653310	29	
	653320	37	
	664680	34	
	480110	13	
	480100	16	
	480090	43	
	653310	48	
	653320	48	
	664680	48	
	75/200	651060	48
		651050	48
		661070	47
651060		48	
651050		48	
661070		48	
651060		37	
651050		48	
651070		48	

#### D. Summary and Conclusion

Overall, an expiration dating period of 37 months seems justifiable for batches for all package types for 75/200 strength.

For 50/200 strength, shorter expiration dating periods of 29 and 13 months appear reasonable for 100-cc bottle and paper/foil/foil/paper strip, respectively.

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*/S/*  
Milton C. Fan, Ph.D.  
Mathematical Statistician

This review consists of 4 pages of text and 1 page of table.

concur: Dr. Huque  
Dr. Smith

*/S/ 10/11/96*  
*/S/ 10/11/96*

cc:

Archival NDA 20-607

HFD-180

HFD-180/Dr. Chen

HFD-180/Dr. Gibbs

HFD-720/Dr. Smith

HFD-720/Dr. Huque

HFD-720/Dr. Fan

Dr. Fan/x73088/mcf/10/11/96

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TABLE 1  
 STATISTICAL ANALYSIS OF 25 °C PRIMARY STABILITY DATA

STRENGTH <sup>1)</sup>	STABILITY NUMBER	LOT NUMBER	ESTIMATED DATING PERIOD IN MONTHS				
			DICLOFENAC SODIUM	MESOPROSTOL	SC-29636 <sup>2)</sup>	SC-37739 <sup>2)</sup>	SC-33188 <sup>2)</sup>
50/200	8754	653310	48	48	48	48	48
	8755	653320	48	48	48	48	48
	8763	664680	48	48	35	48	48
	8752	653310	48	29	48	48	48
	8753	653320	48	37	48	48	48
	8762	664680	48	34	48	48	48
	8676	480110	84	13	84	84	84
	8677	480100	84	16	84	84	84
	8678	480090	79	43	84	84	84
	8756	653310	48	48	48	48	48
75/200	8757	653320	48	48	48	48	48
	8764	664680	48	48	48	48	48
	8745	651060	48	48	48	48	48
	8746	651050	48	48	48	48	48
	8747	651070	48	47	48	48	48
	8742	651060	48	48	48	48	48
	8743	651050	48	48	48	48	48
	8744	651070	48	48	48	48	48
	8748	651060	48	48	37	48	48
	8749	651050	48	48	48	48	48
8750	651070	48	48	48	48	48	

<sup>1)</sup> mg diclofenac sodium/mg mesoprostol  
<sup>2)</sup> Values reported as <0.5 set to 0.25 for calculations

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020607**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-607

Submission Date: August 7th 1997

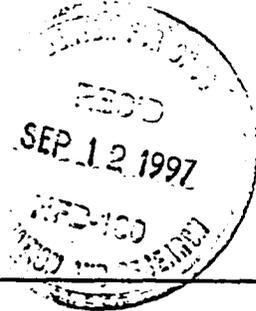
Arthrotec™ Tablets

Diclofenac sodium/Misoprostol

50mg/200mcg and 75 mg/200 mcg

G.D.Searle

Skokie, IL 60077



Reviewer: Lydia C. Kaus, Ph.D.

Type of Submission: Additional studies in support of original NDA

### SYNOPSIS:

The sponsors have completed two pharmacokinetic bioequivalence studies in response to the 3/26/97 letter sent to the sponsors from HFD-180. Specifically the following was stated in the letter:

"The diclofenac in the Arthrotec formulations is not the same as the approved diclofenac, Voltaren. To establish the efficacy of the diclofenac in the Arthrotec formulations proposed for marketing, adequate well-controlled clinical studies providing substantial evidence of safety and efficacy or data that demonstrate bioequivalence to Voltaren must be provided.

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

### RECOMMENDATION:

Since Cytotec and Voltaren are not necessarily given together because of different frequency of dosing (see the current labeling for the individual drugs), comparisons were made for Arthrotec™50 and Arthrotec™75 to Voltaren and Cytotec when given alone.

1. Arthrotec™75 falls outside the 90% CI for the 2 one sided test for Cmax for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec given alone. Arthrotec™75 falls outside the 90% CI for the 2 one sided test for diclofenac AUC as compared to Voltaren alone. Arthrotec™75 is not bioequivalent to Voltaren or Cytotec.

2. Arthrotec™50 falls outside the 90% CI for the 2 one sided test for Cmax for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec given alone. Arthrotec™50 falls within the 90% CI for the 2 one sided test for diclofenac AUC and misoprostol as compared to Voltaren and Cytotec given alone. Arthrotec™50 is not bioequivalent to Voltaren or Cytotec.

The Medical Reviewer should judge these results in the context of the impact on the efficacy and safety of Arthrotec. Please note that no concentration-response relationship for either diclofenac or misoprostol has been submitted to the Agency, therefore any differences in misoprostol or diclofenac plasma levels have to be judged empirically. Lack of bioequivalence or acceptance of

different bioequivalence criteria could be considered, if satisfactory clinically equivalent effects have been shown with formulations that are different in their rate and extent of absorption.

3. The sponsors request for the following dissolution method for misoprostol is acceptable:

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/S/

9/12/97

Lydia C. Kaus, M.S., Ph.D.  
Team Leader, Gastrointestinal and Coagulation Drug  
Products, Division of Pharmaceutical Evaluation II.

FT initialed by     /S/      
Mei-Ling-Chen, Ph.D.  
Director, DPEII

9/12/97

cc:NDA 20-607, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

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**Protocol NN2-97-02-359**

**Title:** Clinical study for an open-label, randomized, five period crossover study to compare the bioequivalence of Arthrotec 75 to marketed Voltaren™ and Cytotec™ tablets in healthy adult subjects under fasting conditions.

**OBJECTIVE**

1. To assess the bioequivalence of Arthrotec™ 75 BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately
2. To assess the bioequivalence of Arthrotec™ 75 BID relative to coadministration of Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID
3. To assess the bioequivalence of coadministered Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately.

**METHODS:**

**Study Design:**

This was an open-label, four treatment, five period crossover study in healthy adult volunteers. Fifty-six subjects were randomized to one of four sequences of treatment administration:

Sequence #	Number of Subjects	Treatment days 1-4	Treatment Days 8-11	Treatment Days 15-18	Treatment Days 22-25	Treatment Days 29-32
1	14	A	D	B	C	A
2	14	B	A	C	D	B
3	14	C	B	D	A	C
4	14	D	C	A	B	D

A = Arthrotec 75 BID

B = Voltaren 75 mg BID Reference arm for diclofenac

C = Cytotec 200 mcg BID Reference arm for misoprostol

D = Voltaren 75 mg BID + Cytotec 200 mcg BID coadministration

**Subjects:**

Fifty-six subjects took part in the study.

**Treatment and Administration:**

A washout period of four days separated each treatment arm. Subjects were confined to a clinical research unit the evening before the first dose until the last pharmacokinetic sample was collected on days 4, 11, 18, 25 and 32. Subjects fasted for at least 2 hours prior to and 2 hours after the doses on days 1-3, 8-10, 15-17, 22-24, and 29-32. Because of protocol deviations concerning processing of the misoprostol acid plasma samples, pharmacokinetic analyses were excluded from data collected during the first period. After the evening dose on Days 3, 10, 17, 24 and 31, subjects remained in an upright posture for at least two hours after dosing. Subjects then fasted overnight for at least 10 hours prior to the next scheduled dose. Blood samples were taken at the following times:

Misoprostol - 10 mL blood sample 15 minutes before first dose, 13 mL blood samples within 15 minutes of last dose and at 10, 15, 20, 30 minutes, 1, 2, and 4 hours post-dose.

Diclofenac - 7 mL blood samples within 15 minutes of first dose and 10 mL blood samples within 15 minutes of last dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours post-dose.

**Formulations/Clinical Supplies:**

- ▶ diclofenac sodium 75 mg with an enteric-coated core of containing misoprostol 200 mcg
  
- ▶ enteric-coated tablets containing diclofenac sodium 75 mg (Voltaren manufactured by Geigy Pharmaceuticals for distribution in the US).
  
- ▶ tablets containing misoprostol 200 mcg (Cytotec, manufactured by Searle for distribution in the US).

**Pharmacokinetic Analysis:**

T<sub>max</sub>, t<sub>lag</sub>, C<sub>max</sub>, C<sub>min</sub>, AUC<sub>0-1q</sub> and AUC<sub>0-inf</sub>, AUC<sub>0-12hr</sub>(diclofenac) and AUC<sub>0-inf</sub>, AUC<sub>0-4hr</sub>(misoprostol) were reported.

Diclofenac:

Misonprostol acid:

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RESULTS from 8/22/97 communication:

Statistical Analysis of diclofenac pharmacokinetic data Study 359:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>DICLOFENAC COMPONENT</b>					
<b>Arthrotec (test) vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	1933.34 (26)	2326.71 (30)	0.82	0.77,0.89	Fail
AUC <sub>last</sub> (ng.hr/mL)	1901.29 (27)	2278.88 (30)	0.83	0.77,0.89	Fail
C <sub>max</sub> (ng/mL)	1582.90 (38)	2166.5 (36)	0.71	0.63,0.80	Fail
<b>Athrotec (test) vs. Voltaren (reference) given with Cytotec</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	2181.44 (34)	2326.71 (31)	0.90	0.84,0.97	Pass
AUC <sub>last</sub> (ng.hr/mL)	1901.29 (27)	2139.43 (35)	0.90	0.84,0.97	Pass
C <sub>max</sub> (ng/mL)	1582.90 (38)	2122.92 (40)	0.76	0.67,0.85	Fail
<b>Voltaren (test) given with Cytotec vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	2181.44(34)	2326.71(30)	0.92	0.86,0.99	Pass
AUC <sub>last</sub> (ng.hr/mL)	2139.43 (35)	2278.88 (30)	0.92	0.86,0.99	Pass
C <sub>max</sub> (ng/mL)	2122.92 (40)	2166.5 (36)	0.94	0.83,1.06	Fail

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>MISOPROSTOL ACID COMPONENT</b>					
<b>Arthrotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
<b>Athrotec (test) vs. Voltaren given with Cytotec (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	725.92 (58)	0.89	0.79,1.01	Fail
<b>Voltaren given with Cytotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	442.29(37)	492.70(44))	1.09	1.02,1.18	Pass
AUC <sub>last</sub> (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
C <sub>max</sub> (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC<sub>0-4</sub> denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC<sub>0-12</sub> for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC<sub>0-12</sub> represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUC<sub>inf</sub> is less reliable where the data points on the terminal phase of the curve are not well represented.

**RESULTS from 9/10/97 communication:**

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>MISOPROSTOL ACID COMPONENT</b>					
<b>Arthrotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
<b>Athrotec (test) vs. Voltaren given with Cytotec (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	725.92 (58)	0.89	0.79,1.01	Fail
<b>Voltaren given with Cytotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	442.29(37)	492.70(44))	1.09	1.02,1.18	Pass
AUC <sub>last</sub> (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
C <sub>max</sub> (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC<sub>0-4</sub> denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC<sub>0-12</sub> for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC<sub>0-12</sub> represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUC<sub>inf</sub> is less reliable where the data points on the terminal phase of the curve are not well represented.

RESULTS from 9/10/97 communication:

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol

acid, day 11, Cytotec arm) and subject 28 (diclofenac, Voltaren arm).

Subject	Treatment	C <sub>max</sub>	T <sub>max</sub>	AUC <sub>0-12</sub>	AUC <sub>inf</sub>	AUC <sub>last</sub>	AUC <sub>0-4</sub>
18, 8/22/97	A,D	1390	2.55	2567.92	2514.18	2480.04	n/a
18, 9/10/97	A,D	1390	2.55	2585.33	2586.09	2480.04	n/a
26 8/22/97	A,M	465	0.5	n/a	684.19	468.79	468.79
26 9/10/97	A,M	465	0.5	n/a	680.75	468.79	468.79
30 8/22/97	C	1270	0.17	n/a	594.23	586.33	612.79
30 9/10/97	C	1270	0.17	n/a	594.23	586.33	612.79
28 8/22/97	V	2040	0	3563.68	3582.35	3522.28	
28 9/10/97	V	1960	2.05	3563.68	3582.35	3522.28	

A=Arthrotec, D=diclofenac component, M=misoprostol acid component, C=Cytotec, V=Voltaren, n/a=not applicable.

There were no differences shown for subject 30 between the datasets as checked by this Reviewer.

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**Results from re-run using 9/10/97 dataset:**

**Statistical Analysis of diclofenac pharmacokinetic data Study 359:**

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>DICLOFENAC COMPONENT</b>					
<b>Arthrotec (test) vs. Voltaren alone (reference)</b>					
AUC0-12 (ng.hr/mL)	1933.34 (26)	2326.71 (30)	0.82	0.77,0.89	Fail
AUCinf (ng.hr/mL)	1997.12 (25)	2333.19 (31)	0.85	0.80,0.90	Pass
Cmax (ng/mL)	1582.90 (38)	2164.9 (36)	0.71	0.63,0.80	Fail
<b>Athrotec (test) vs. Voltaren (reference) given with Cytotec</b>					
AUC0-12 (ng.hr/mL)	2181.44 (34)	2333.19 (31)	0.90	0.84,0.97	Pass
AUCinf (ng.hr/mL)	2189.98(31)	2333.19(31)	0.92	0.87,0.98	Pass
Cmax (ng/mL)	1582.90 (38)	2038(47)	0.76	0.67,0.85	Fail
<b>Voltaren (test) given with Cytotec vs. Voltaren alone (reference)</b>					
AUC0-12 (ng.hr/mL)	2181.44(34)	2326.71(30)	0.92	0.86,0.99	Pass
AUCinf (ng.hr/mL)	2189.98 (31)	2333.19 (31)	0.92	0.86,0.99	Pass
Cmax (ng/mL)	2038.00 (47)	2164.9 (36)	0.94	0.83,1.06	Pass

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Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>MISOPROSTOL ACID COMPONENT</b>					
<b>Arthrotec (test) vs. Cytotec alone (reference)</b>					
AUC0-4 (pg.hr/mL)	438.50(34)	492.70(44)	0.90	0.84,0.96	Pass
AUCinf (pg.hr/mL)	475.75 (37)	528.02 (43)	0.90	0.83,0.98	Pass
Cmax (pg/mL)	677.31 (62)	823.95 (60)	0.81	0.71,0.91	Fail
<b>Athrotec (test) vs. Voltaren given with Cytotec (reference)</b>					
AUC0-4 (pg.hr/mL)	438.50(34)	442.29(37)	0.99	0.92,1.06	Pass
AUCinf (pg.hr/mL)	475.75 (37)	459.18 (37)	1.00	0.92,1.08	Pass
Cmax (pg/mL)	677.31 (62)	725.92 (58)	0.89	0.79,1.01	Fail
<b>Voltaren given with Cytotec (test) vs. Cytotec alone (reference)</b>					
AUC0-4 (pg.hr/mL)	442.29(37)	492.70(44)	0.91	0.85,0.97	Pass
AUCinf (pg.hr/mL)	459.18 (37)	528.02(43)	0.90	0.84,0.96	Pass
Cmax (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.83,0.97	Pass

Note that AUC0-4 denotes the area-under-the curve measured from 0 to 4 hours and AUCinf notes the area-under-the curve extrapolated to infinity

The AUC0-4 or AUC0-last is more appropriate measure for bioequivalence testing. AUCinf is less reliable where the data points on the terminal phase of the curve are not well represented.

**CONCLUSIONS:**

Arthrotec 75 falls outside the 90% CI for the 2 one sided test for Cmax for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec. Arthrotec 75 falls outside the 90% CI for the 2 one sided test for diclofenac AUC as compared to Voltaren alone. Arthrotec 75 is not bioequivalent to Voltaren nor Cytotec.

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**Protocol NN2-97-02-360**

**Title:** Clinical study for an open-label, randomized, four period crossover study to compare the bioequivalence of Arthrotec 50 to marketed Voltaren™ and Cytotec™ tablets in healthy adult subjects under fasting conditions.

**OBJECTIVE**

1. To assess the bioequivalence of Arthrotec™ 50 BID relative to Voltaren™ 50 mg BID or Cytotec™ 200 mcg BID given separately
2. To assess the bioequivalence of Arthrotec™ 50 BID relative to coadministration of Voltaren™ 50 mg BID and Cytotec™ 200 mcg BID
3. To assess the bioequivalence of coadministered Voltaren™ 50 mg BID and Cytotec™ 200 mcg BID relative to Voltaren™ 50 mg BID or Cytotec™ 200 mcg BID given separately.

**Demographics:**

38 male, 14 female subjects

Mean age = 27 yr

Mean B.Wt. = 71.8 Kg

**METHODS:**

**Study Design:**

This was an open-label, four treatment, four period crossover study in healthy adult volunteers. Fifty-two subjects were randomized to one of four sequences of treatment administration:

Sequence #	Number of Subjects	Treatment days 1-4	Treatment Days 8-11	Treatment Days 15-18	Treatment Days 22-25
1	13	A	D	B	C
2	13	B	A	C	D
3	13	C	B	D	A
4	13	D	C	A	B

- A = Arthrotec 50 BID
- B = Voltaren 50 mg BID Reference arm for diclofenac
- C = Cytotec 200 mcg BID Reference arm for misoprostol
- D = Voltaren 50 mg BID + Cytotec 200 mcg BID coadministration

**Subjects:**

Fifty-two subjects took part in the study.

**Treatment and Administration:**

A washout period of four days separated each treatment arm. Subjects were confined to a clinical research unit the evening before the first dose until the last pharmacokinetic sample was collected on days 4, 11, 18 and 25. Subjects fasted for at least 2 hours prior to and 2 hours after the doses on days 1-3, 8-10, 15-17, and 22-24. After the evening dose on Days 3, 10, 17 and 24, subjects remained in an upright posture for at least two hours after dose. Subjects then fasted overnight for at least 10 hours prior to the next scheduled dose. Blood samples were taken at the following times:

Misoprostol - 10 mL blood sample 15 minutes before first dose, 13 mL blood samples within 15 minutes of last dose and at 10, 15, 20, 30 minutes, 1, 2, and 4 hours post-dose.

Diclofenac - 7 mL blood samples within 15 minutes of first dose and 10 mL blood samples within 15 minutes of last dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours post-dose.

**Formulations/Clinical Supplies:**

- ▶ 11 mm combination tablets containing an aqueous enteric-coated core of diclofenac sodium 50 mg with an outer mantle containing misoprostol 200 mcg

Batch No. 787900

- ▶ enteric-coated tablets containing diclofenac sodium 50 mg (Voltaren manufactured by Geigy Pharmaceuticals for distribution in the US). Lot no. LT4061
- ▶ tablets containing misoprostol 200 mcg (Cytotec, manufactured by Searle for distribution in the US). Lot no. 6P554

**Pharmacokinetic Analysis:**

Tmax, tlag, Cmax, Cmin, AUC0-lqc and AUC0-inf, AUC0-12hr(diclofenac) and AUC0-inf and AUC0-4hr(misoprostol) were reported.

**Analytical Methods:**

**RESULTS**

Statistical Analysis of diclofenac pharmacokinetic data, Study 360:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>DICLOFENAC COMPONENT</b>					
<b>Arthrotec (test) vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	1175.85(29)	1324.64(32)	0.89	0.81,0.98	Pass
AUC <sub>last</sub> (ng.hr/mL)	1149.95 (29)	1290.70 (33)	0.90	0.81,0.99	Pass
C <sub>max</sub> (ng/mL)	950.98 (45)	1294.2 (46)	0.72	0.61,0.84	Fail
<b>Athrotec (test) vs. Voltaren (reference) given with Cytotec</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	1175.85(29)	1181.02(35)	1.04	0.94,1.14	Pass
AUC <sub>last</sub> (ng.hr/mL)	1901.29 (27)	1144.40 (36)	1.05	0.95,1.16	Pass
C <sub>max</sub> (ng/mL)	1582.90 (38)	1190.39 (50)	0.84	0.72,0.98	Fail
<b>Voltaren (test) given with Cytotec vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	1181.02(35)	1324.64(32)	0.86	0.78,0.95	Fail
AUC <sub>last</sub> (ng.hr/mL)	1290.70 (33)	1290.70 (33)	0.86	0.78,0.94	Fail
C <sub>max</sub> (ng/mL)	1294.2 (46)	1294.2 (46)	0.86	0.73,1.00	Fail

Statistical Analysis of misoprostol acid pharmacokinetic data Study 360:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>MISOPROSTOL ACID COMPONENT</b>					
<b>Arthrotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	400.88(28)	451.61(30)	0.89	0.84,0.95	Pass
AUC <sub>last</sub> (pg.hr/mL)	367.89 (32)	419.75 (34)	0.88	0.83,0.95	Pass
C <sub>max</sub> (pg/mL)	607.61 (35)	714.83 (34)	0.84	0.78,0.91	Fail
<b>Athrotec (test) vs. Voltaren given with Cytotec (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	400.88(28)	419.38(30)	0.96	0.91,1.02	Pass
AUC <sub>last</sub> (pg.hr/mL)	367.89 (32)	391.01 (31)	0.94	0.87,1.00	Pass
C <sub>max</sub> (pg/mL)	607.61 (35)	631.64 (36)	0.96	0.89,1.03	Pass
<b>Voltaren given with Cytotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	419.38(30)	451.61(30)	0.93	0.87,0.99	Pass
AUC <sub>last</sub> (pg.hr/mL)	391.01 (31)	419.75 (34)	0.95	0.88,1.01	Pass
C <sub>max</sub> (pg/mL)	631.64 (36)	714.83 (34)	0.88	0.80,0.94	Pass

**CONCLUSIONS**

Arthrotec50 falls outside of the 90% CI for the 2 one sided test for C<sub>max</sub> for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec given alone. Arthrotec 50 falls within the 90% CI for the 2 one sided test for diclofenac AUC and misoprostol as compared to Voltaren and Cytotec given alone. Arthrotec 50 is not bioequivalent to Voltaren nor Cytotec.

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**Dissolution Update:**

The following dissolution conditions were proposed by the Agency in the November 22, 1996 letter sent to the sponsors:

**Diclofenac Sodium:**

**Misoprostol:**

This was discussed and agreed upon with the Chemistry Reviewer.

<b>Study 359 - Arthrotec 75 mg</b>														
<b>DICLOFENAC</b>														
<b>Study 359 Arthrotec vs. Voltaren</b>														
	<b>ls mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric mean ratio</b>	<b>90% Confidence</b>		<b>std error (difference)</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>		<b>Interval</b>				
AUC12	7.715478	7.528058	-0.18742	-0.25827	-0.11657	2242.794	1859.491	0.829096	0.7723878	0.88997	0.042644	51	93	
AUCL	7.694534	7.510471	-0.18406	-0.25491	-0.11322	2196.31	1827.074	0.831883	0.7749892	0.89295	0.0426406	51	93	
CMAx	7.627758	7.287447	-0.34031	-0.45767	-0.22295	2054.439	1461.834	0.711549	0.6327536	0.80016	0.0706409	51	93	
<b>Study 359 Arthrotec vs. Combo</b>														
	<b>ls mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric mean ratio</b>	<b>90% Confidence</b>		<b>std error (difference)</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>		<b>Interval</b>				
AUC12	7.635245	7.528058	-0.10719	-0.17895	-0.03542	2069.877	1859.491	0.898358	0.8361471	0.9652	0.0431948	51	93	
AUCL	7.615912	7.510471	-0.10544	-0.1772	-0.03368	2030.245	1827.074	0.899928	0.8376087	0.96688	0.0431944	51	93	
CMAx	7.566253	7.287447	-0.27881	-0.39769	-0.15993	1931.888	1461.834	0.756687	0.6718738	0.85221	0.0715534	51	93	
<b>Study 359 Combo vs. Voltaren</b>														
	<b>ls mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric mean ratio</b>	<b>90% Confidence</b>		<b>std error (difference)</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>		<b>Interval</b>				
AUC12	7.715478	7.635245	-0.08023	-0.15269	-0.00778	2242.794	2242.794	0.922901	0.8583958	0.99225	0.0436256	51	96	
AUCL	7.694534	7.615912	-0.07862	-0.15107	-0.00617	2196.31	2030.245	0.924389	0.8597847	0.99385	0.0436221	51	96	
CMAx	7.627758	7.566253	-0.06151	-0.18153	0.058522	2054.439	1931.888	0.940348	0.8339915	1.06027	0.072267	51	96	
<b>MISOPROSTOL</b>														
<b>Study 359 Arthrotec vs. Cytotec</b>														
	<b>ls mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric mean ratio</b>	<b>90% Confidence</b>		<b>std error (difference)</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>		<b>Interval</b>				
AUC4	6.122448	6.01605	-0.1064	-0.17197	-0.04083	455.9794	409.9561	0.899067	0.842008	0.95999	0.0394779	51	96	
AUCL	6.073294	5.961415	-0.11188	-0.18268	-0.04108	434.1083	388.1592	0.894153	0.8330361	0.95975	0.0426278	51	96	
CMAx	6.553249	6.337804	-0.21545	-0.33637	-0.09452	701.5199	565.5531	0.806183	0.7143586	0.90981	0.0728078	51	96	

<b>Study 359 Arthrotec vs. Combo</b>													
	Is mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
UC4	6.028676	6.01605	-0.01263	-0.07861	0.053363	415.1649	409.9561	0.987454	0.9243966	1.05481	0.0397309	51	96
UCL	5.965989	5.961415	-0.00457	-0.07583	0.06668	389.9384	388.1592	0.995437	0.9269768	1.06895	0.042901	51	96
MAX	6.453404	6.337804	-0.1156	-0.2373	0.0061	634.8598	565.5531	0.890832	0.7887545	1.00612	0.0732744	51	96
<b>Study 359 Combo vs. Cytotec</b>													
	Is mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
UC4	6.028676	6.122448	0.093772	0.027783	0.15976	415.1649	415.1649	1.098309	1.0281731	1.17323	0.0397309	51	96
UCL	6.073294	5.965989	-0.10731	-0.17856	-0.03605	434.1083	389.9384	0.898251	0.836475	0.96459	0.042901	51	96
MAX	6.553249	6.453404	-0.09985	-0.22155	0.021855	701.5199	634.8598	0.904978	0.8012796	1.0221	0.0732744	51	96
<b>Study 360 - Arthrotec 50 mg</b>													
<b>Study 360 Arthrotec vs. Voltaren</b>													
	Is mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
UC12	7.14592	7.031967	-0.11395	-0.2091	-0.0188	1268.918	1132.256	0.8923	0.8113135	0.98137	0.0572155	47	85
UCL	7.117644	7.009005	-0.10864	-0.20661	-0.01066	1233.541	1106.553	0.897054	0.8133331	0.98939	0.0589158	47	85
MAX	7.089433	6.762873	-0.32656	-0.47988	-0.17324	1199.227	865.1245	0.721402	0.6188592	0.84094	0.092195	47	85
<b>Study 360 Arthrotec vs. Combo</b>													
	Is mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
UC12	6.99547	7.031967	0.036497	-0.05952	0.132513	1091.676	1132.256	1.037172	0.9422181	1.14169	0.0577373	47	85
UCL	6.962336	7.009005	0.046669	-0.0522	0.145539	1056.098	1106.553	1.047776	0.9491392	1.15666	0.0594531	47	85
MAX	6.936692	6.762873	-0.17382	-0.32853	-0.0191	1029.359	865.1245	0.84045	0.7199779	0.98108	0.0930359	47	85

Study 360 Combo vs. Voltaren														
	Is mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
UC12	7.14592	6.99547	-0.15045	-0.24563	-0.05527	1268.918	1091.676	0.860321	0.7822114	0.94623	0.0572347	47	85	
UCL	7.117644	6.962336	-0.15531	-0.25332	-0.0573	1233.541	1056.098	0.856151	0.7762219	0.94431	0.0589355	47	85	
MAX	7.089433	6.936692	-0.15274	-0.30597	0.000483	1199.227	1029.359	0.858352	0.7364119	1.00048	0.0922259	47	93	
MISOPROSTOL														
Study 360 Arthrotec vs. Cytotec														
	Is mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
UC4	6.061401	5.949839	-0.11156	-0.16957	-0.05355	428.9759	383.6915	0.894438	0.8440281	0.94785	0.0348906	47	87	
UCL	5.974725	5.852956	-0.12177	-0.19081	-0.05273	393.3598	348.2623	0.885353	0.8262891	0.94864	0.0415275	47	87	
MAX	6.519337	6.346648	-0.17269	-0.24805	-0.09733	678.1289	570.5768	0.841399	0.7803194	0.90726	0.0453292	47	87	
Study 360 Arthrotec vs. Combo														
	Is mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
UC4	5.989754	5.949839	-0.03991	-0.09743	0.017596	399.3162	383.6915	0.960871	0.9071699	1.01775	0.0345918	47	87	
UCL	5.918932	5.852956	-0.06598	-0.13443	0.002474	372.0142	348.2623	0.936153	0.874217	1.00248	0.0411719	47	87	
MAX	6.387441	6.346648	-0.04079	-0.11551	0.033924	594.3334	570.5768	0.960028	0.890912	1.03451	0.044941	47	87	
Study 360 Combo vs. Cytotec														
	Is mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
UC4	6.061401	5.989754	-0.07165	-0.12919	-0.0141	428.9759	428.9759	0.930859	0.8788066	0.986	0.0346114	47	87	
UCL	5.974725	5.918932	-0.05579	-0.12428	0.012697	393.3598	372.0142	0.945735	0.8831308	1.01278	0.0411952	47	87	
MAX	6.519337	6.387441	-0.1319	-0.20666	-0.05714	678.1289	594.3334	0.876431	0.8132992	0.94446	0.0449665	47	87	

<b>Study 359 - Arthrotec 75 mg</b>														
<b>DICLOFENAC</b>														
<b>Study 359 Arthrotec vs. Voltaren</b>														
	<b>Is mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric</b>	<b>90% Confidence</b>		<b>std error</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>	<b>mean rati</b>	<b>Interval</b>		<b>(difference)</b>		
AUC12	7.715471	7.528186	-0.18729	-0.2581	-0.11648		2242.78	1859.729	0.829207	0.7725217	0.89005	0.0426204	51	93
AUCinf	7.722827	7.565755	-0.15707	-0.21478	-0.09936		2259.337	1930.926	0.854643	0.8067193	0.90541	0.0346825	51	81
CMAx	7.627032	7.287468	-0.33956	-0.4576	-0.22153		2052.948	1461.864	0.71208	0.6327981	0.8013	0.071048	51	93
<b>Study 359 Arthrotec vs. Combo</b>														
	<b>Is mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric</b>	<b>90% Confidence</b>		<b>std error</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>	<b>mean rati</b>	<b>Interval</b>		<b>(difference)</b>		
AUC12	7.635233	7.528186	-0.10705	-0.17877	-0.03532		2069.852	1859.729	0.898484	0.8362975	0.96529	0.0431709	51	93
AUCinf	7.649383	7.565755	-0.08363	-0.14336	-0.02389		2099.349	1930.926	0.919774	0.8664407	0.97639	0.0359004	51	81
CMAx	7.566281	7.287468	-0.27881	-0.39781	-0.15982		1931.943	1461.864	0.756681	0.6717898	0.8523	0.0716238	51	93
<b>Study 359 Combo vs. Voltaren</b>														
	<b>Is mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric</b>	<b>90% Confidence</b>		<b>std error</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>	<b>mean rati</b>	<b>Interval</b>		<b>(difference)</b>		
AUC12	7.715471	7.635233	-0.08024	-0.15266	-0.00782		2242.78	2242.78	0.922896	0.8584252	0.99221	0.0436014	51	96
AUCinf	7.722827	7.649383	-0.07344	-0.13451	-0.01238		2259.337	2099.349	0.929188	0.8741448	0.9877	0.0367002	51	81
CMAx	7.627032	7.566281	-0.06075	-0.1809	0.059394		2052.948	1931.943	0.941058	0.8345223	1.06119	0.0723381	51	96
<b>MISOPROSTOL</b>														
<b>Study 359 Arthrotec vs. Cytotec</b>														
	<b>Is mean (log)</b>		<b>difference</b>	<b>90% Confidence</b>			<b>geometric mean</b>		<b>geometric</b>	<b>90% Confidence</b>		<b>std error</b>	<b>n</b>	<b>df (MSE)</b>
	<b>reference</b>	<b>test</b>		<b>Interval</b>			<b>reference</b>	<b>test</b>	<b>mean rati</b>	<b>Interval</b>		<b>(difference)</b>		
AUC4	6.122424	6.016611	-0.10581	-0.17146	-0.04017		455.9687	410.1861	0.899593	0.8424335	0.96063	0.0395256	51	96
AUCinf	6.185707	6.077802	-0.10791	-0.19132	-0.02449		485.7562	436.0696	0.897713	0.8258715	0.9758	0.0501883	51	90
CMAx	6.553249	6.337804	-0.21545	-0.33637	-0.09452		701.5199	565.5531	0.806183	0.7143586	0.90981	0.0728078	51	96

<b>Study 359 Arthrotec vs. Combo</b>													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean rati	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
AUC4	6.028685	6.016611	-0.01207	-0.07814	0.053994	415.1689	410.1881	0.987998	0.9248327	1.05548	0.0397789	51	96
AUCinf	6.08179	6.077802	-0.00399	-0.08618	0.078208	437.8122	436.0696	0.99602	0.917425	1.08135	0.0494575	51	90
CMAx	6.453404	6.337804	-0.1156	-0.2373	0.0061	634.8598	565.5531	0.890832	0.7887545	1.00612	0.0732744	51	96
<b>Study 359 Combo vs. Cytotec</b>													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean rati	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
AUC4	6.122424	6.028685	-0.09374	-0.15981	-0.02767	455.9687	455.9687	0.910521	0.8523083	0.97271	0.0397789	51	96
AUCinf	6.185707	6.08179	-0.10392	-0.18708	-0.02078	485.7562	437.8122	0.9013	0.8293788	0.97946	0.0500382	51	90
CMAx	6.553249	6.453404	-0.09985	-0.22155	0.021855	701.5199	634.8598	0.904978	0.8012796	1.0221	0.0732744	51	96

APPEARS THIS WAY  
ON ORIGINAL

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW****NDA 20-607****Submission Date: August 7th 1997****Arthrotec™ Tablets****Diclofenac sodium/Misoprostol****50mg/200mcg and 75 mg/200 mcg****G.D.Searle****Skokie, IL 60077****Reviewer: Lydia C. Kaus, Ph.D.****Type of Submission: Additional studies in support of original NDA****SYNOPSIS:**

The sponsors have completed two pharmacokinetic bioequivalence studies in response to the 3/26/97 letter sent to the sponsors from HFD-180. Specifically the following was stated in the letter:

"The diclofenac in the Arthrotec formulations is not the same as the approved diclofenac, Voltaren. To establish the efficacy of the diclofenac in the Arthrotec formulations proposed for marketing, adequate well-controlled clinical studies providing substantial evidence of safety and efficacy or data that demonstrate bioequivalence to Voltaren must be provided.

.....

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

**RECOMMENDATION:**

Since Cytotec and Voltaren are not necessarily given together because of different frequency of dosing (see the current labeling for the individual drugs), comparisons were made for Arthrotec™50 and Arthrotec™75 to Voltaren and Cytotec when given alone.

1. Arthrotec™75 falls outside the 90% CI for the 2 one sided test for Cmax for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec given alone. Arthrotec™75 falls outside the 90% CI for the 2 one sided test for diclofenac AUC as compared to Voltaren alone. Arthrotec™75 is not bioequivalent to Voltaren or Cytotec.
2. Arthrotec™50 falls outside the 90% CI for the 2 one sided test for Cmax for both the misoprostol and diclofenac component as compared to Voltaren and Cytotec given alone. Arthrotec™50 falls within the 90% CI for the 2 one sided test for diclofenac AUC and misoprostol as compared to Voltaren and Cytotec given alone. Arthrotec™50 is not bioequivalent to Voltaren or Cytotec.

The Medical Reviewer should judge these results in the context of the impact on the efficacy and safety of Arthrotec. Please note that no concentration-response relationship for either diclofenac or misoprostol has been submitted to the Agency, therefore any differences in misoprostol or diclofenac plasma levels have to be judged empirically. Lack of bioequivalence or acceptance of

different bioequivalence criteria could be considered, if satisfactory clinically equivalent effects have been shown with formulations that are different in their rate and extent of absorption.

3. The sponsors request for the following dissolution method for misoprostol is acceptable:

- APPEARS THIS WAY  
ON ORIGINAL

/S/

11/2/97

Lydia C. Kaus, M.S., Ph.D.  
Team Leader, Gastrointestinal and Coagulation Drug  
Products, Division of Pharmaceutical Evaluation II.

FT initialed by             
Mei-Ling Chen, Ph.D.  
Director, DPEII

/S/

9/12/97

cc:NDA 20-607,- HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

APPEARS THIS WAY  
ON ORIGINAL

**Protocol NN2-97-02-359**

**Title:** Clinical study for an open-label, randomized, five period crossover study to compare the bioequivalence of Arthrotec™ 75 to marketed Voltaren™ and Cytotec™ tablets in healthy adult subjects under fasting conditions.

**OBJECTIVE**

1. To assess the bioequivalence of Arthrotec™ 75 BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately
2. To assess the bioequivalence of Arthrotec™ 75 BID relative to coadministration of Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID
3. To assess the bioequivalence of coadministered Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately.

**METHODS:**

**Study Design:**

This was an open-label, four treatment, five period crossover study in healthy adult volunteers. Fifty-six subjects were randomized to one of four sequences of treatment administration:

Sequence #	Number of Subjects	Treatment days 1-4	Treatment Days 8-11	Treatment Days 15-18	Treatment Days 22-25	Treatment Days 29-32
1	14	A	D	B	C	A
2	14	B	A	C	D	B
3	14	C	B	D	A	C
4	14	D	C	A	B	D

- A = Arthrotec 75 BID
- B = Voltaren 75 mg BID Reference arm for diclofenac
- C = Cytotec 200 mcg BID Reference arm for misoprostol
- D = Voltaren 75 mg BID + Cytotec 200 mcg BID coadministration



**RESULTS from 8/22/97 communication:**

**Statistical Analysis of diclofenac pharmacokinetic data Study 359:**

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>DICLOFENAC COMPONENT</b>					
<b>Arthrotec (test) vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	1933.34 (26)	2326.71 (30)	0.82	0.77,0.89	Fail
AUC <sub>last</sub> (ng.hr/mL)	1901.29 (27)	2278.88 (30)	0.83	0.77,0.89	Fail
C <sub>max</sub> (ng/mL)	1582.90 (38)	2166.5 (36)	0.71	0.63,0.80	Fail
<b>Athrotec (test) vs. Voltaren (reference) given with Cytotec</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	2181.44 (34)	2326.71 (31)	0.90	0.84,0.97	Pass
AUC <sub>last</sub> (ng.hr/mL)	1901.29 (27)	2139.43 (35)	0.90	0.84,0.97	Pass
C <sub>max</sub> (ng/mL)	1582.90 (38)	2122.92 (40)	0.76	0.67,0.85	Fail
<b>Voltaren (test) given with Cytotec vs. Voltaren alone (reference)</b>					
AUC <sub>0-12</sub> (ng.hr/mL)	2181.44(34)	2326.71(30)	0.92	0.86,0.99	Pass
AUC <sub>last</sub> (ng.hr/mL)	2139.43 (35)	2278.88 (30)	0.92	0.86,0.99	Pass
C <sub>max</sub> (ng/mL)	2122.92 (40)	2166.5 (36)	0.94	0.83,1.06	Fail

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
<b>MISOPROSTOL ACID COMPONENT</b>					
<b>Arthrotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
<b>Athrotec (test) vs. Voltaren given with Cytotec (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUC <sub>last</sub> (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	Pass
C <sub>max</sub> (pg/mL)	677.31 (62)	725.92 (58)	0.89	0.79,1.01	Fail
<b>Voltaren given with Cytotec (test) vs. Cytotec alone (reference)</b>					
AUC <sub>0-4</sub> (pg.hr/mL)	442.29(37)	492.70(44))	1.09	1.02,1.18	Pass
AUC <sub>last</sub> (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
C <sub>max</sub> (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC<sub>0-4</sub> denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC<sub>0-12</sub> for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC<sub>0-12</sub> represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUC<sub>inf</sub> is less reliable where the data points on the terminal phase of the curve are not well represented.

**RESULTS from 9/10/97 communication:**

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol