between the two treatments rather than the least squares mean improvement from baseline since they felt that there would not be enough room for improvement in this non-flare trial with a stable denominator in Q.) The Sponsor also did a subset analysis of patients based on the target joint studied (i.e., knee or hip) that showed no significant treatment differences existed for any of the 3 primary efficacy assessments for patients with either OA of the hip or knee studied in this trial. The results of the Week 4 evaluable cohort analysis (not shown) were similar to the results of the Week 4 ITT analysis shown in Table 13 (see above).

The intent-to-treat (ITT) analysis of the secondary efficacy parameters demonstrated that there were no statistically significant differences between the 2 treatment groups for 3 out of the 3 primary efficacy variables (Articular Index of Joint Tenderness: p=0.489; Change in Functional Capacity: p=0.414; Patient's Assessment of Joint Pain: p=0.457).

Reviewer's Comments

This trial followed essentially the same protocol as Study IN2-89-02-298 except that the patients enrolled in this trial underwent endoscopic evaluation as part of the safety monitoring and efficacy assessment for the misoprostol component of the combination test drug. Therefore, the same comments made by this reviewer re: Study IN2-89-02-298 related to trial design, data analysis (i.e., the calculation of the Q statistic) and the interpretations of trial results apply here. Besides the endoscopic evaluation, the fact that there were a similar number of dropouts due to adverse events for both treatment groups and no dropouts during this trial from either treatment group due to a lack of efficacy sets this trial apart from its sister study. It is highly unusual not to have dropouts during a NSAID trial due to a lack of efficacy. This may be related to the study's non-flare design. In summary, this trial demonstrated that the diclofenac/misoprostol combination was comparable in terms of efficacy to that of diclofenac/placebo in the treatment of patients with OA of the hip or knee.

A COMPARISON OF THE EFFICACY AND UPPER GASTROINTESTINAL SAFETY OF DICLOFENAC 50 MG/MISOPROSTOL 200 MCG V.S. PIROXICAM 10 MG OR NAPROXEN 375 MG BID IN THE TREATMENT OF PATIENTS WITH OSTEOARTHRITIS

Protocol IN2-90-02-321

Design:

This was a multi-center, double-blind trial with 3 parallel treatment arms in which patients with American College of Rheumatology (ACR) functional class I-III OA of the knee and/or hip, were randomized to receive either a fixed combination of diclofenac 50

mg/misoprostol 200 mcg BID (Arthrotec I), piroxicam 10 mg BID or naproxen 375 mg BID for 4 weeks. Prior to being randomized to one of the 3 comparative treatment groups, patients had to have active pain in the target joint, and undergo a 10 -day washout period of all ongoing therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). Once randomized, patients had to have an endoscopic examination of the stomach and duodenum performed within 7 days of the first dose of study medication demonstrating no active GI disease (defined as ≥ 10 erosions or any ulcerative damage in either region). No other treatment with anti-ulcer medications or antacids were permitted for the duration of the trial. Rescue acetaminophen was permitted for the short-term treatment of headaches and other mild ailments, but could not be used within 24-hours of an efficacy evaluation.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 2 and 4 of the study. All patients were evaluated for the following three primary efficacy parameters for OA: the Physician's Global Assessment and the Patient's Global Assessment of Arthritis Condition via categorical scales; and the OA Severity Index. The OA Severity Index was a composite score, based on a maximum score of 24, comprised of various patient self-assessments related to the following: severity of OA pain, walking distance and activities of daily living. Secondary efficacy variables were also performed and included: a Patient's Assessment of Joint Pain via a 10 cm visual analogue scale (VAS), and a Functional Capacity Classification. Safety was assessed by upper gastrointestinal (GI) endoscopy, routine lab analyses, physical exams and adverse event monitoring. Upper GI endoscopy examinations were performed on all patients at baseline and at the final study visit (Week 4). (Note: A discussion of the trial's endoscopy findings can be found in the GI medical officer's safety review.) Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, all 3 treatment groups were comparable in terms of background characteristics such as race, gender, age, height and weight. The majority of the patients entered were Caucasian (81%) and female (76%), with a mean age of 59.6 years There were no significant differences noted between the groups in the target joint affected or in disease duration (7.3 years).

With the exception of a statistically significant difference noted between the treatment groups at the baseline evaluation for the OA Severity Index ($p=0.024$), the other 4 efficacy variables at baseline were not significantly different (Physician's or Patient's Global Assessments $p \geq 0.284$, Functional Capacity $p=0.059$, or the Patient's Assessment of Joint Pain $p=0.328$).

Fifty-one (51) international investigators entered 1 or more patients. A total of 643 patients were randomized into the trial as follows: 158 patients were treated with diclofenac/misoprostol, 164 were treated with piroxicam, 157 were treated with naproxen. Sixty-five (65) patients discontinued the study due to a variety of reasons as

shown in the following table, Table 14. (See below.) The majority of patients who dropped out prematurely from the 3 treatment groups did so due to adverse events, the incidence of which was not found to be statistically significant on comparison between the active treatment groups, with the piroxicam group having the lowest number of drop-outs due to adverse events. (See Table 14 below.) The naproxen treatment group had the greatest number of total premature discontinuations (20/210, 9.5%) which were again mainly due to adverse events. (Refer to Table 14.)

Table 14 - Reasons For Premature Trial Discontinuation From Study IN2-92-06-321

Reason	Diclofenac/ Misoprostol (N=216)	Piroxicam (N=217)	Naproxen (N=210)	Total
Lack of Efficacy:	0(0%)	0(0%)	0(0%)	0
Adverse Event:	18(8%)	10(6%)	20(10%)	48
Protocol Deviation:	5(2%)	3(1%)	4(2%)	12
Lost to Follow-Up:	0(0%)	4(2%)	1(1%)	2
Total:	23(11%)	17(8%)	25(12%)	65

For all 3 treatment groups, the mean compliance with medications was greater than 95%, and no significant differences ($p \geq 0.265$) were noted between the treatment groups over time.

Efficacy:

The primary endpoint analysis was the Week 4 visit. An intent-to-treat analysis (ITT), or last observation carried forward as compared to baseline, of the 3 primary efficacy variables evaluated is presented in the following table, Table 15 (see below).

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Table 15- Results of the Week 4 ITT Analysis Change from Baseline and Least Squares Mean (LSM) of the 3 Primary Efficacy Variables Evaluated In Study IN2-92-06-321

Efficacy Variable	Diclofenac/ Misoprostol (N=216)	Piroxicam (N=178)	Naproxen (N=210)	P-Value*
Physician's Global:				
Categorical-***				p=0.706
Improved	25%	21%	21%	
Unchanged	67%	72%	69%	
Worsened	0%	0%	0%	
Unknown	9%	7%	10%	
Baseline Mean	3.42	3.31	3.37	
Q and q[C.I.]**		1.03[1.00,1.06]	1.01[0.99,1.04]	
LSM	2.42	2.48	2.53	
Q and q[C.I.]**		0.98[0.92,1.04]	0.96[0.89,1.02]	
Patient's Global:				
Categorical-***				p=0.512
Improved	36%	31%	28%	
Unchanged	55%	62%	62%	
Worsened	0%	0%	0%	
Unknown	9%	7%	10%	
Baseline Mean	3.53	3.44	3.45	
Q and q[C.I.]**		1.03[0.99,1.06]	0.98[0.92,1.04]	
LSM	2.48	2.57	2.64	
Q and q[C.I.]**		0.96[0.90,1.03]	0.94[0.88,1.01]	
OA Severity Index:				
Mean Change****	-4.27	-3.19	-3.79	p=0.015
Baseline Mean	12.21	11.35	11.88	
Q and q[C.I.]		1.08[1.02,1.13]	1.03[0.98,1.08]	
LSM	8.82	9.05	9.19	
Q and q[C.I.]		0.97[0.89,1.06]	0.96[0.88,1.05]	

* Kruskal-Wallis no-parametric test. Test statistic is Chi-square distributed.

**Note: The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Diclofenac/Misoprostol and active rather than the least squares mean improvement from baseline. The rationale for using the actual mean score rather than the mean improvement by the Sponsor was that the room for improvement would be too small for a stable denominator in Q since the patients were not flared at baseline. The numbers in the bracket are the lower and upper 95% confidence intervals of Q.

*** Note: "Improved" or "worsened" from baseline was pre-defined by the Sponsor as a decrease or increase, respectively, of 2 or more units.

**** Note: A negative value denotes improvement from baseline.

This trial demonstrated that there were no statistically significant differences between the 3 treatment groups for 2 out of the 3 primary efficacy variables (Physician's Global Assessment: p=0.706; Patient's Global: p=0.151; p=0.281). A significant difference between the 3 treatment groups for the OA Severity Index (p=0.015) was noted on 3-way comparison. (See Table 15 above.) On pairwise comparison, treatment with diclofenac/misoprostol was shown to be significantly better than piroxicam (p=0.004) in terms of the OA Severity Index, but it was not found to be statistically different when compared to naproxen (p=0.211). In terms of comparability, the diclofenac/misoprostol treatment group captured 6 out of the 6 Q ratios and q[L] values for the primary efficacy variables on pairwise comparison with the 2 active comparators. (Refer to Table 15 shown above for the actual numerical values.) (Note: In calculating the Q values for this trial, the Sponsor used the actual mean at baseline or the least squares mean at Week 4 between the two treatments rather than the least squares mean improvement from baseline since they felt that there would not be enough room for improvement in this non-flare trial with a stable denominator in Q.) The results of the Week 4 evaluable cohort analysis (not shown) were similar to the results of the Week 4 ITT analysis shown in Table 15 (see above). Again on a three-way comparison, a significant difference between the 3 treatment groups for the OA Severity Index (p=0.015) was noted. When looked at via pairwise comparison this statistically significant difference was only noted to exist on comparison of the diclofenac/misoprostol group versus the piroxicam group (p=0.003), and not on comparison of the diclofenac/misoprostol group to the naproxen group (p=0.123).

The intent-to-treat (ITT) analysis of the secondary efficacy parameters demonstrated that there were no statistically significant differences between the 3 treatment groups for either of the 2 secondary efficacy variables (Change in Functional Capacity: p=0.286; Patient's Assessment of Joint Pain: p=0.768).

Reviewer's Comments

This trial followed essentially the same protocol as Studies IN2-89-02-298 and IN2-89-02-296 except that the patients enrolled in this trial also underwent endoscopic evaluation as part of the safety monitoring and efficacy assessment for misoprostol component of the combination test drug. Therefore, the same comments made by this reviewer re: the preceding 2 trials as related to the interpretation of trial results, design, and data analysis (i.e., the calculation of the Q statistic) apply here as well.

Once again no patients dropped out of this trial from either of the 3 treatment groups because of a lack of efficacy is rather remarkable for an NSAID trial. This may have been directly influenced by the trial's non-flare design. The fact that piroxicam had the lowest number of dropouts due to adverse events may have also been affect by the dose regimen used to administer it in this trial (i.e., BID). It is usually administered once a day as a single dose of 20 mg due to its long half-life. Although the 3 treatment groups were found to have unequal baseline scores for the OA Severity Index, splitting the dose of piroxicam may have been an additional reason why the

diclofenac/misoprostol combination was found to be significantly better than piroxicam for this efficacy parameter at the final visit (Week 4). The OA Severity Index, which is a composite evaluation tool that assesses many aspects of joint pain as related to activity and inactivity, is complex and difficult to interpret. It is usually not used as a primary efficacy parameter as it was in this trial since it becomes redundant when used with the Patient's Global assessment. Since NSAIDs mainly exert an analgesic effect in the treatment of OA, patients randomized to the piroxicam treatment group may not have received the full analgesic effect that may be achieved with single dose administration, and experienced breakthrough pain as the day went on. Although this finding of superiority was found to be statistically significant on data analysis, this medical reviewer feels it is clinically irrelevant based on the above stated reasons. This is supported by failing to find a significant difference to exist between treatments on the pairwise and three-way comparisons for the Patient's Assessment of Joint Pain, which was used as a secondary efficacy parameter instead of a primary variable in this study.

Overall, this trial demonstrated that treatment with the diclofenac/misoprostol combination was equivalent to that of piroxicam or naproxen in the treatment of patients with OA of the hip or knee.

Section II - Rheumatoid Arthritis Trials

DOUBLE-BLIND, PLACEBO-CONTROLLED COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF DICLOFENAC 75 MG BID, DICLOFENAC 50 MG/MISOPROSTOL 200 MCG (ARTHROTEC I) TID, AND DICLOFENAC 75 MG/MISOPROSTOL 200 MCG (ARTHROTEC II) BID IN TREATING THE SIGNS AND SYMPTOMS OF RHEUMATOID ARTHRITIS.

Protocol NN2-95-ST-352

Design:

This was a multi-center, double-blind, placebo-controlled trial with 4 parallel treatment arms in which patients with functional class I-III rheumatoid arthritis as defined by ACR criteria were randomized to receive either diclofenac 75 mg b.i.d., Arthrotec I (diclofenac 50 mg/misoprostol 200 mcg) t.i.d., Arthrotec II (diclofenac 75 mg/misoprostol 200 mcg) b.i.d., or placebo for 12 weeks. Prior to being randomized to one of the 4 comparative treatment groups, patients had to demonstrate a clinical flare of their RA during a 3 to 14 -day washout period of all ongoing therapy with NSAIDs or analgesics. Rescue acetaminophen was permitted for the short-term treatment of headaches and other mild ailments, but could not be used within 24-hours of an efficacy evaluation. Continuation of treatment with stable doses of background antirheumatic drugs (i.e., gold, azathioprine, methotrexate, hydroxychloroquinine, systemic corticosteroids) was permitted, but intra-articular injections of corticosteroids was prohibited for the duration of the trial.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 2 , 6 and 12 of the study. All patients were evaluated for the following three primary efficacy parameters for OA: the Physician's and the Patient's Global Assessments of Arthritis via categorical scales, and the Physician's Assessment of Joint Tenderness and Swelling. Secondary efficacy variables were also performed and included: a Functional Capacity Classification, Incidence and Time to Withdrawal Due to Lack Efficacy, Duration of Morning Stiffness, Patient's Assessment of Arthritis Pain via 10 cm VAS, a Health Assessment Questionnaire (HAQ), the SF-36 Health Survey and the Paulus Index of Responder's Analysis. Safety was assessed by routine lab analyses, physical exams and adverse event monitoring. Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, all 4 treatment groups were comparable in terms of background characteristics such as race, gender, age, height and weight. The majority of the patients entered were Caucasian (89%) and female (74%), with a mean age of 56 years The mean duration of disease was 11.5 years, and was not significantly different between the groups.

There were no significant differences noted between the treatment groups at the baseline evaluation for the Physician's or Patient's Global Assessments ($p \geq 0.779$), Number of Tender Joints ($p=0.489$), Number of Swollen Joints ($p=0.672$), Functional Capacity ($p=0.931$), Patient's Assessment of Arthritis Pain ($p=0.397$), Duration of Morning Stiffness ($p=0.736$), ESR ($p=0.916$), HAQ Scores ($p=0.876$), or the 8 domains of the SF-36 Health Survey ($p \geq 0.248$).

Disposition:

Twenty (20) investigators in the United States and Canada entered 1 or more patients. A total of 380 patients were randomized into the trial as follows: 107 patients were treated with diclofenac BID, 107 were treated with Arthrotec I TID, 111 were treated with Arthrotec II BID, and 55 were treated with placebo. One hundred thirty-two (132) patients discontinued the study due to a variety of reasons as shown in Table 16. (See below.) The placebo treatment group had the greatest number of overall premature discontinuations (42%) which were not unexpectedly due to a lack of efficacy. The numbers of patients that discontinued from the 3 active treatment groups were similar. (See Table 16 below.) The majority of patients who dropped out prematurely from the 3 active treatment groups did so due to lack of efficacy although the Arthrotec I group had the highest incidence of drop-outs due to adverse events. (Refer to Table 16 below.)

Table 16 - Reasons For Premature Trial Discontinuation From Study NN2-95-ST-352

Reason	Diclofenac 75 mg b.i.d (N=107)	Arthrotec I t.i.d. (N=107)	Arthrotec II b.i.d. (N=111)	Placebo (N=55)
Lack of Efficacy:	15(14%)	16(15%)	23(21%)	21(38%)
Adverse Event:	10(9%)	18(17%)	11(10%)	0(0%)
Protocol Deviation:	4(4%)	5(5%)	4(4%)	2(4%)
Lost to Follow-Up:	0(0%)	1(1%)	2(2%)	0(0%)
Total:	29(27%)	40(37%)	40(36%)	23(42%)

Overall the incidence of adverse events experienced by patients during the trial was similar for the 3 active treatment groups: 69.2% (74/107) for the diclofenac 75 mg BID treatment group, 76.6% (82/107) for the Arthrotec I TID treatment group, 73.9% (82/111) for the Arthrotec II BID treatment group. The incidence of adverse events in the placebo group was relatively high: 47.3% (26/55). (Note: The Sponsor attributed this finding as an artifact of data collection via the daily diary cards kept by the patients. See safety review by HFD-180 medical reviewer.) The types of adverse events reported by patients were also similar for the 3 active treatments, and predominantly involved the gastrointestinal tract as shown in the following table, Table 17. (See below.)

Table 17 - Incidences of the Most Frequently Reported Drug-Related Adverse Events for Study NN2-95-ST-352

Adverse Event	Diclofenac 75 mg b.i.d (N=154) N (%)	Arthrotec I t.i.d. (N=152) N (%)	Arthrotec II b.i.d. (N=175) N (%)	Placebo (N=91) N (%)	Total (N=572) N (%)
Dyspepsia	21(19.6)	24(22.4)	23(20.7)	4(7.3)	72(18.9)
Abdominal Pain	18(16.8)	29(27.1)	19(17.1)	4(7.3)	70(18.4)
Diarrhea	14(13.1)	27(25.2)	20(18.0)	3(5.5)	64(16.8)
Headache	16(15.0)	18(16.8)	17(15.3)	13(23.6)	64(16.8)
Flatulence	5(4.7)	10(9.3)	10(9.0)	1(1.8)	26(6.8)
Constipation	3(2.8)	5(4.7)	3(2.7)	0(3.3)	11(2.9)
Nausea	9(8.4)	10(9.3)	14(12.6)	3(5.5)	36(9.5)
Vomiting	4(3.7)	6(5.6)	6(5.4)	1(1.8)	17(4.5)

(Note: This review is limited to the assessment of drug efficacy. For further discussion of safety see the HFD-180 medical officer's safety review.)

No significant differences were noted between the groups in terms of compliance with study medication which was greater than 86% for all 4 treatment groups during all treatment periods.

Efficacy:

An intent-to-treat analysis (ITT), with the last observation carried forward as compared to baseline for missing data is presented in the following table, Table 18 (see below), for the 4 primary efficacy variables evaluated. (Note: The Week 2 evaluations will not be presented or discussed in this review since NSAID efficacy trials are usually evaluated based on the data results of Week 4 or later.)

Table 18- Results of the Weeks 6 and 12 ITT Analysis Change from Baseline and Least Squares Mean (LSM) Change of the 4 Primary Efficacy Variables Evaluated In Study NN2-95-ST-352

	Diclofenac 75 mg b.i.d (N=107)		Arthrotec I t.i.d. (N=107)		Arthrotec II b.i.d. (N=111)		Placebo (N=91)	
Efficacy Variable	**Wk 6**	**Wk 12**	**Wk 6**	**Wk 12**	**Wk 6**	**Wk 12**	**Wk 6**	**Wk 12**
Physician's Global:								
Categorical-*								
Improved	28.0%	28.0%	27.1%	25.2%	28.2%	22.7%	20.0%	14.5%
Unchanged	71.0%	70.1%	72.9%	74.8%	70.9%	76.4%	76.4%	81.8%
Worsened	0.9%	1.9%	0.0%	0.0%	0.9%	0.9%	3.6%	3.6%
Baseline Mean	3.5	3.5	3.6	3.6	3.4	3.4	3.5	3.5
LSM Change **	-0.92	-0.90	-0.92	-0.89	-0.97	-0.81	-0.66	-0.55
Patient's Global:								
Categorical-*								
Improved	27.1%	25.2%	31.8%	28.0%	30.9%	26.4%	29.1%	20.0%
Unchanged	72.0%	72.9%	67.3%	69.2%	68.2%	72.7%	67.3%	76.4%
Worsened	0.9%	1.9%	0.9%	2.8%	0.9%	0.9%	3.6%	3.6%
Baseline Mean	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
LSM Change**	-0.79	-0.71	-0.80	-0.73	-0.90	-0.75	-0.63	-0.59
Joint Tenderness:								
Baseline Mean	28.2	28.2	31.5	31.5	29.4	29.4	29.9	29.9
LSM Change**	-10.16	-10.98	-8.61	-8.82	-13.34	-12.72	-4.81	-4.09
Joint Swelling:								
Baseline Mean	20.1	20.1	23.0	23.0	22.6	22.6	20.8	20.8
LSM Change**	-6.48	-6.22	-5.86	-5.53	-8.57	-8.03	-3.53	-3.29

* Note: "Improved" or "worsened" from baseline was pre-defined by the Sponsor as a decrease or increase, respectively, of 2 or more units.
** Note: A negative value denotes improvement from baseline.

The p-values for the principal or primary pairwise comparisons and their

respective Q-ratios and qL values to determine the comparability of the test drug(s) with an active control for Weeks 6 and 12 evaluations are shown in Table 19 (see below). [Note: For RA trials an acceptable Q ratio and qL value are $0.80 \leq Q \leq 1.20$ and ≥ 0.70 respectively.] This trial demonstrated that there were no statistically significant differences between the diclofenac treated group versus either the Arthrotec I or II treatment groups for all 4 primary efficacy variables at either the Week 6 or 12 evaluations. (Refer to Table 19 below for the p-values for these pairwise comparisons.) Comparability of Arthrotec II versus diclofenac was shown by the capture of 4 out of the 4 Q ratios and q[L] values for the primary efficacy variables at both the Week 6 and 12 time points. Arthrotec I was comparable to diclofenac in only 2 out of the 4 primary efficacy variables (Physician's and Patient's Global) at both of these time point evaluations. (See Table 19 below.) While diclofenac 75 mg BID was not shown to be a significantly more effective treatment than placebo for any of the 4 primary efficacy variables at the Week 2 (not shown) or Week 6 evaluations, a statistically significant difference was shown for this treatment group for 2 out of the 4 primary efficacy variables, the LSM analysis for both the Week 12 Physician's Global (p=0.022) and the Tender Joint Assessments (p=0.017). No significant difference between diclofenac versus placebo for the Week 12 Physician's Global categorical analysis was noted (p=0.139). (Refer to Table 19 below for a complete listing of the p-values).

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Table 19 - Table of P-Values, Q-Ratios and qL values from the ITT Analysis of the Primary Pairwise Comparisons in Study NN2-95-ST-352

Efficacy Variable	Diclofenac b.i.d. vs. Placebo		Arthrotec I t.i.d. vs. Diclofenac		Arthrotec II b.i.d. vs. Diclofenac	
	Wk 6	Wk 12	Wk 6	Wk 12	Wk 6	Wk 12
Physician's Global:						
Categorical	p=0.286	p=0.139	p=0.594	p=0.314	p=1.000	p=0.534
LSM	p=0.069	p=0.022*	p=0.983	p=0.944	p=0.666	p=0.456
Q [qL]			1.00[0.77]	0.99[0.75]	1.06[0.82]	0.90[0.66]
Patient's Global:						
Categorical	p=0.450	p=0.624	p=0.754	p=0.793	p=0.826	p=0.823
LSM	p=0.486	p=0.461	p=0.930	p=0.882	p=0.397	p=0.754
Q [qL]			1.01[0.74]	1.03[0.71]	1.14[0.84]	1.06[0.73]
Tender Joints:						
LSM Change	p=0.062	p=0.017*	p=0.511	p=0.363	p=0.174	p=0.459
Q [qL]			0.73[0.42]	0.69[0.40]	1.32[0.92]	1.16[0.81]
Swollen Joints:						
LSM Change	p=0.151	p=0.165	p=0.715	p=0.692	p=0.214	p= 0.294
Q [qL]			0.77[0.44]	0.75[0.39]	1.21[0.81]	1.17[0.75]

*Statistically significant p-value

Secondary pairwise comparisons via this ITT analysis for the 4 primary efficacy variables showed that while Arthrotec II was significantly more effective than placebo at Week 6 in 3 out of the 4 primary efficacy variables (Physician's Global: p = 0.029; Joint Tenderness: p=0.003; Joint Swelling: p=0.014), it was only able to achieve statistical significance against placebo in 2 out of the 4 parameters at the Week 12 evaluation (Joint Tenderness: p=0.003 and Joint Swelling: p=0.024). (See table 20 below.) Although a statistically significant difference between Arthrotec I and placebo was demonstrated for only 1 out 4 assessments at Week 12 (Physician's Global Assessment p=0.025), and for none of the 4 assessments at Week 6, it was shown to be significantly better than Arthrotec II for Joint Tenderness (p=0.043) at Week 6. (See Table 20 below.)

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

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

* Statistically significant p-values

The Sponsor also performed a second ITT in which treatment by investigator was an added interaction term. In this analysis, diclofenac, Arthrotec I and II all consistently beat placebo ($p \leq 0.039$) in 3 out of the 4 efficacy parameters (Physician's Global, Tender Joints and Swollen Joints) at the Week 6 and 12 evaluations.

The evaluable cohort analysis (not shown) performed by the Sponsor demonstrated no significant difference between diclofenac, Arthrotec I and II versus placebo in any of the 4 primary efficacy variables, but a numerical trend was noted in favor of the 3 treatments over placebo.

In terms of secondary efficacy assessments, all 3 active treatments were significantly better than placebo ($p \leq 0.0.016$) for Dropouts Due to Lack of Efficacy, at the Week 6 Patient's Assessment of Arthritis Pain ($p \leq 0.021$) and at the Week 6 HAQ Score ($p \leq 0.045$). The diclofenac treated group was also significantly better than placebo for the Week 12 HAQ Score ($p \leq 0.05$) . Arthrotec I was significantly better than placebo for the Week 6 and 12 Functional Capability Assessments ($p \leq 0.002$) while Arthrotec II was only significantly better than placebo at the Week 12 evaluation for this assessment (p=0.002). Arthrotec I also was also significantly better than diclofenac for the Week 6 Functional Capability Assessment (p=0.036). Arthrotec II was shown to be significantly better than placebo at both Weeks 6 and 12 for the Paulus Index (p=0.011, p=0.010 respectively) while diclofenac was only significantly better than placebo at Week 12 (p=0.007). Only Arthrotec II was shown to be significantly different from placebo on the SF-36 at Weeks 6 and 12 for physical functioning (p=0.013 and p=0.010) and bodily pain (p=0.025 and p=0.028) while diclofenac was significantly different from placebo at both the Week 6 and 12 evaluations for bodily pain (p=0.041 and p=0.043). No significant differences were demonstrated for any pairwise comparison at Weeks 6 and 12 for the ESR or Duration of Morning Stiffness.

Reviewer's Comments

The results of this trial are conflicting and somewhat confusing. While Arthrotec I and II were shown to be comparable to the dose of diclofenac tested (75 mg BID) in some of the parameters, the diclofenac treatment group failed to statistically beat placebo convincingly at the Week 6 and Week 12 time point evaluations for the principle or primary pairwise comparisons. This raises questions concerning the trial's sensitivity and the validity of the effectiveness of the active comparator (diclofenac) used in this trial. (Note: The formulation of diclofenac used in this study was not the innovator's formulation.) In addition, while Arthrotec II (containing 75 mg of diclofenac given BID) was able to statistically beat placebo in 3 out of 4 efficacy parameters (the Physician's Global, the Tender Joint Count and the Swollen Joint Count) at Week 6 in the secondary pairwise comparisons, it was shown to be significantly better than placebo in only 2 out of the 4 parameters (the Tender Joint Count and the Swollen Joint Count) at Week 12. Arthrotec I's (containing 50 mg of diclofenac given TID) performance in the secondary comparisons was even worse. While Arthrotec I failed to statistically beat placebo in any of the efficacy parameters at the Week 6 evaluation, it was shown to be significantly better than Arthrotec II at the Week 6 evaluation for Joint Tenderness ($p=0.043$) but was only able to show a significant difference against placebo in 1 out of the 4 efficacy parameters (Physician's Global) at Week 12. These findings failed to be supported by the evaluable cohort analysis where only numerical trends in favor of the 3 active treatments were noted for all 4 efficacy variables. Yet when the Sponsor controlled for treatment by investigator on another ITT analysis of the trial's data, all 3 active treatments statistically beat placebo in 3 out of the 4 parameters.

The above analyses were all based on pooled data from the 20 centers that entered patients into this trial. Placebo response between individual centers was highly variable (see HFD-550 biostatistician's efficacy review), but could only be appreciated when the mean change for each of the 4 primary efficacy parameters was plotted out. This could have had a potential role in the weak performances of both diclofenac and Arthrotec I, as well as Arthrotec II. (See biostatistician's efficacy review for these graphs.) Thus by directly failing to validate the effectiveness of the formulation of active comparator (diclofenac) used against the placebo-control, one cannot truly state that either Arthrotec I and II is statistically better than placebo.

This trial does provide some evidence that the 3 active treatments are clinically effective in the treatment of rheumatoid arthritis. This is based on the findings of the secondary parameters which demonstrated that treatment with all 3 active medications was statistically better than placebo for overall Dropouts Due to Lack of Efficacy ($p \leq 0.016$), as well as the significant differences as compared to placebo for all 3 treatments' Week 6 HAQ Scores ($p \leq 0.05$). The secondary parameters also helped to confirm that Arthrotec II is probably better than Arthrotec I in the treatment of rheumatoid arthritis by demonstrating a significant difference against placebo for the Paulus Index at both the Week 6 and 12 time point evaluations, while Arthrotec I failed

to do so. Diclofenac was also shown to be significantly better than placebo at Week 12, but not at Week 6 by the Paulus Index. (Note: The Paulus Index is a validated efficacy variable that has sometimes been employed as a primary parameter in other rheumatoid arthritis trials.)

The results of this trial may all be related to the size of the diclofenac dose tested. The recommended dose range for the innovator's formulation of diclofenac sodium is 150 to 200 mg a day in divided doses in the treatment of rheumatoid arthritis. The Sponsor only studied the lower limit of this dose range in this trial. Other factors to be taken into account are related to patient compliance with test medications, disease severity of the patients enrolled (i.e., Functional Capacity), and drug bioequivalence and bioavailability of the 2 Arthrotec formulations and the formulation of the active comparator. (See the biopharmaceutical reviewer's review for this NDA for further discussion of bioequivalence and bioavailability.) This reviewer finds it very odd that despite the fact that the total daily doses of both Arthrotec I and II tested in this trial were the same (150 mg of diclofenac), treatment with Arthrotec II tended to be more efficacious than with Arthrotec I. Since compliance with study medication was greater than 86% for most of the trial for all 3 arms, and of the patients enrolled were either Class II or III in terms of Functional Capacity, it is highly unlikely that either compliance or disease severity were important factors in the final outcome of this study.

At best, this trial offers some supportive evidence that Arthrotec II is an effective treatment for rheumatoid arthritis based on the results of the secondary comparisons against placebo and the secondary efficacy parameters. The evidence presented in this trial for Arthrotec I 's effectiveness in rheumatoid arthritis is even less convincing.

A COMPARISON OF DICLOFENAC/MISOPROSTOL AND DICLOFENAC/PLACEBO IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Protocol IN2-89-02-292

Design:

This was a multi-center, double-blind, placebo-controlled trial with 2 parallel treatment arms in which patients with functional class I-III rheumatoid arthritis as defined by ACR criteria were randomized to receive either diclofenac 50 mg/misoprostol 200 mcg (Arthrotec I) b.i.d. or t.i.d. or diclofenac 50 mg/placebo b.i.d. or t.i.d. for 12 weeks. Prior to being randomized to one of the 2 comparative treatment groups, patients had to have been on a stable regimen of diclofenac 50 mg BID or TID for at least one month. Continuation of treatment with stable doses of background antirheumatic drugs (i.e., gold, azathioprine, methotrexate, hydroxychloroquine, systemic corticosteroids) was permitted, but intra-articular injections of corticosteroids was prohibited for the duration of the trial.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 4 , 8 and 12 of the study. All patients were evaluated for the following four

primary efficacy parameters for RA: the Physician's and the Patient's Global Assessments of Arthritis via categorical scales, and the Physician's Assessment of Joint Tenderness and Swelling. Secondary efficacy variables were also performed and included: a Functional Capacity Classification, Duration of Morning Stiffness and ESR. Safety was assessed by routine lab analyses, physical exams and adverse event monitoring. Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, both treatment groups were comparable in terms of background characteristics such as race, gender, age, height and weight. The majority of the patients entered were Caucasian (98%) and female (74%), with a mean age of 56.4 years The mean duration of disease was 7.8 years for the diclofenac/misoprostol group versus 9.3 years for the diclofenac/placebo group, and was found to be significantly different (p=0.019).

Disposition:

Thirty-six (36) international investigators entered 1 or more patients. A total of 346 patients were randomized into the trial as follows: 177 patients were treated with diclofenac/misoprostol (Arthrotec I) and 169 were treated with diclofenac/placebo. Fifty-four (54) patients discontinued the study due to a variety of reasons as shown in Table 21. (See below.) The numbers of patients that discontinued from the 2 treatment groups prematurely were similar (21%). (See Table 21 below.) The majority of patients who dropped out prematurely from the 2 active treatment groups did so due to adverse events. (See Table 21 below.)

Table 21 - Reasons For Premature Trial Discontinuation From Study IN2-89-02-292

Reason	Diclofenac 50 mg/ Placebo BID-TID (N=169)	Diclofenac 50 mg/ Misoprostol 200 mcg BID-TID (N=177)	Total
Lack of Efficacy:	5(3.0%)	7(4.0%)	11
Adverse Event:	26(15.4%)	28(15.8%)	54
Protocol Deviation:	3(1.8%)	2(1.1%)	5
Lost to Follow-Up:	2(1.2%)	1(0.5%)	3
Total:	36(21.3%)	38(21.5%)	74

No significant differences were noted between the 2 groups in terms of compliance with study medication which was greater than 91% for both treatment groups during all treatment periods. The numbers and proportions of patients who

changed their study medicine dosage regimens was not statistically different between the 2 groups at the Week 4 and Week 8 visits.

Efficacy:

An intent-to-treat analysis (ITT), with last observation carried forward as compared to baseline for missing data is presented in the following table, Table 22 (see below), for the 4 primary efficacy variables evaluated at the Weeks 4, 8 and 12 evaluations. Improvement and/or worsening was predefined by the Sponsor as a changed in 2 or more units for the categorical analysis for the Physician's and Patient's Global Assessments. The ITT analysis demonstrated that there were no significant differences between the 2 treatment groups at any of the time point evaluations with the exception of the Week 8 Physician's Global Assessment (p=0.044). The results of the evaluable cohort analysis were similar to that of the ITT analysis with the exception that the Week 8 Physician's Global Assessment was no longer statistically significant (p=0.105). (See Table 22 below.)

Table 22- Results of the ITT Analysis of Weeks 4, 8 and 12 From Baseline of the 4 Primary Efficacy Variables Evaluated In Study IN2-89-02-292

	Diclofenac/Misoprostol 50 mg/200 mcg BID-TID			Diclofenac/Placebo 50 mg/0 mcg BID-TID			P-value		
Outcome[a]	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12
Assessment of Joint Tenderness/ Pain									
Improved	13%	11%	12%	14%	12%	13%			
Unchanged	74%	60%	58%	77%	70%	60%	0.743	0.116	0.893
Worsened	11%	12%	9%	8%	7%	7%			
Unknown	2%	17%	21%	1%	11%	20%			
Assessment of Joint Swelling									
Improved	11%	11%	14%	15%	16%	14%			
Unchanged	73%	60%	52%	72%	60%	57%	0.693	0.232	0.521
Worsened	13%	12%	14%	12%	13%	9%			
Unknown	2%	17%	21%	1%	11%	20%			
Physician's Global Assessment									
Improved	5%	5%	7%	3%	1%	2%			
Unchanged	92%	77%	72%	94%	88%	79%	0.444	0.044*	0.080
Worsened	1%	1%	1%	2%	1%	0%			
Unknown	2%	17%	21%	1%	11%	19%			
Patient's Global Assessment									
Improved	3%	6%	7%	4%	3%	3%			
Unchanged	92%	75%	71%	92%	83%	75%	0.781	0.127	0.226
Worsened	2%	2%	1%	4%	4%	3%			
Unknown	2%	17%	21%	1%	11%	19%			

[a] Change from baseline
* Statistically significant at the 5% level

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The Q-static and its corresponding 95% confidence limit, the q[L], were calculated for the 4 primary efficacy parameters at the Week 4 time point using the ratio of the actual mean baseline or least squares mean improvement from baseline. (Note: The Sponsor justified doing these calculations this way on the basis of the previously stated rationalization that there was not enough room to demonstrate improvement with a stable Q denominator due to the trial's non-flare design.) Comparability between the diclofenac/misoprostol treatment group and the diclofenac/placebo treatment group was demonstrated by capturing all 4 Q values and their corresponding q[L] values for the primary efficacy parameters shown as follows: Physician's Global: Mean Baseline- 1.05 [1.00, 1.11], Least Square Mean - 1.04 [0.98, 1.11]; Patient's Global: Mean Baseline - 1.03 [0.98, 1.09], Least Square Mean - 1.04 [0.97, 1.12]; Tender Joints: Mean Baseline - 0.99 [0.88, 1.12],Least Square Mean - 1.03[0.88,1.20]; and Joint Swelling: Mean Baseline - 1.14 [1.00, 1.29], Least Square Mean - 1.21 [1.05, 1.41].

Analysis of the secondary efficacy variables of Duration of Morning Stiffness and ESR showed that while there were no significant differences between the 2 treatment groups at any of the 3 evaluation time points in terms of the Duration of Morning Stiffness, there was a statistically significant difference on comparison of the diclofenac/misoprostol versus the diclofenac/placebo treatment groups at the Week 4 time point assessment for ESR (p=0.010). This difference was not noted at the Weeks 8 and 12 time point evaluations for this parameter (p=0.162 and p=0.267, respectively).

Reviewer's Comments

This was the first efficacy trial done by the Sponsor for the fixed combination of diclofenac/misoprostol. Although the trial did show that treatment with diclofenac/misoprostol was comparable to that with diclofenac/placebo, care must be applied in the interpretation of the trial's results. First, the dosage regimens were not fixed for the duration of the trial. Second, the protocol was again of a non-flare design that induced the Sponsor to use a modified method to calculate the Q-statistic. Thirdly, only patients who had been on stable regimens of diclofenac for at least 30 days prior to trial entry were permitted to enter the trial. This may have introduced selection bias into both the safety and efficacy outcomes of the trial by allowing patients that were able to tolerate and respond to diclofenac to be entered. Thus, it may be more correct in stating that the trial demonstrated that treatment with the fixed combination of diclofenac/misoprostol was comparable to that with diclofenac/placebo in "maintaining" a therapeutic response to diclofenac. This is supported by the exceptionally high values obtained for the Q and q[L] for the 4 primary efficacy variables, including Joint Swelling which past experience has proven difficult to capture in NSAID trials, and by the low numbers of patients that demonstrated any changed from baseline. The presence of a placebo-control arm in this trial would have been helpful in clarifying these issues. Therefore this medical reviewer believes that this trial offers only supportive evidence of the fixed combination diclofenac/misoprostol efficacy in the

treatment of rheumatoid arthritis.

A COMPARISON OF EFFICACY AND UPPER GASTROINTESTINAL SAFETY OF DICLOFENAC/MISOPROSTOL AND DICLOFENAC /PLACEBO IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS.

Protocol IN2-89-02-289

Design:

This was a multi-center, double-blind, placebo-controlled trial with 2 parallel treatment arms in which patients with rheumatoid arthritis as defined by ACR criteria were randomized to receive either diclofenac 50 mg/misoprostol 200 mcg (Arthrotec I) BID or TID or diclofenac 50 mg/placebo BID or TID for 12 weeks. Once randomized, patients had to have an endoscopic examination of the stomach and duodenum performed within 7 days of the first dose of study medication demonstrating no active GI disease (defined as $\geq$ 10 erosions or any ulcerative damage in either region). No other treatment with anti-ulcer medications or antacids were permitted for the duration of the trial. Rescue acetaminophen was permitted for the short-term treatment of headaches and other mild ailments, but could not be used within 24-hours of an efficacy evaluation. Continuation of treatment with stable doses of background antirheumatic drugs (i.e., gold, azathioprine, methotrexate, hydroxychloroquine, systemic corticosteroids) was permitted, but intra-articular injections of corticosteroids was prohibited for the duration of the trial.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 4 , 8 and 12 of the study. All patients were evaluated for the following two primary efficacy parameters for RA: the Physician's and the Patient's Global Assessments of Arthritis via categorical scales. Secondary efficacy variables were also performed and included: a Functional Capacity Classification, Duration of Morning Stiffness and ESR. Safety was assessed by endoscopy, routine lab analyses, physical exams and adverse event monitoring. (Note: For discussion of the endoscopy results see the HFD-180 medical officer's safety review.) Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, both treatment groups were comparable in terms of background characteristics such as race, gender, age, height and weight. The majority of the patients entered were Caucasian (82%) and female (77%), with a mean age of 53.3 years The mean duration of disease was 9.2 years and was not found to be significantly different between the treatment groups.

Disposition:

Forty-three (43) international investigators entered 1 or more patients. A total of 339 patients were randomized into the trial as follows: 164 patients were treated with diclofenac/misoprostol and 175 were treated with diclofenac/placebo. Sixty-three (63) patients discontinued the study due to a variety of reasons as shown in Table 23. (See below.) The numbers of patients that discontinued from the 2 treatment groups prematurely were similar. (See Table 23 below.) The diclofenac/misoprostol treatment group had the greatest number of overall premature discontinuations (19.5%). The majority of patients who dropped out prematurely from the 2 active treatment groups did so due to adverse events as shown in Table 23 (see below.)

Table 23 - Reasons For Premature Trial Discontinuation From Study IN2-89-02-289

Reason	Diclofenac 50 mg/ Placebo b.i.d.-t.i.d. (N=175)	Diclofenac 50 mg/ Misoprostol 200 mcg b.i.d.-t.i.d. (N=164)	Total
Lack of Efficacy:	4(2.3%)	6(3.7%)	10
Adverse Event:	15(8.6%)	18(11.0%)	33
Protocol Deviation:	5(2.9%)	4(2.4%)	9
Lost to Follow-Up:	7(4.0%)	4(2.4%)	11
Total:	31(17.7%)	32(19.5%)	63

No significant differences were noted between the 2 groups in terms of compliance with study medication which was greater than 94% for both treatment groups during all treatment periods. The numbers and proportions of patients who changed their study medicine dosage regimens was not statistically different between the 2 groups at the Weeks 4, 8 and 12 visits.

Efficacy:

An intent-to-treat analysis (ITT), with last observation carried forward as compared to baseline for missing data is presented in the following table, Table 24 (see below), for the 2 primary efficacy variables evaluated at the Weeks 4, 8 and 12 time points. Improvement and/or worsening was predefined by the Sponsor as a changed in 2 or more units for the categorical analysis for both the Physician's and Patient's Global Assessments.

Table 24- Results of the Weeks 4, 8 and 12 ITT Categorical Analysis Change from Baseline of the 2 Primary Efficacy Variables Evaluated In Study IN2-89-02-289

	% of Patients								
	Diclofenac/Misoprostol 50 mg/200 mcg BID-TID			Diclofenac/Placebo 50 mg/0 mcg BID-TID			P-value		
Outcome[a]	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12
Physician's Global Assessment									
Improved	4%	7%	5%	7%	8%	7%			
Unchanged	90%	81%	76%	90%	81%	78%	0.300	0.434	0.663
Worsened	2%	1%	2%	1%	3%	1%			
Unknown	5%	11%	16%	3%	8%	14%			
Patient's Global Assessment									
Improved	5%	9%	8%	8%	8%	8%			
Unchanged	89%	76%	74%	87%	81%	77%	0.430	0.717	0.904
Worsened	1%	4%	2%	2%	3%	2%			
Unknown	5%	11%	16%	3%	8%	14%			

[a] Change from baseline

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The ITT analysis did not find any statistically significant differences between the 2 treatment groups. The results of the evaluable cohort analysis were similar to that of the ITT analysis.

The Q-static and its corresponding 95% confidence limit, the q[L], were calculated for the 2 primary efficacy parameters at the Week 4 time point using the ratio of the actual mean baseline or least squares mean improvement from baseline. (Note: The Sponsor justified doing these calculations this way on the basis of the previously stated rationalization that there was not enough room to demonstrate improvement with a stable Q denominator due to the trial's non-flare design.) Comparability between the diclofenac/misoprostol treatment group and the diclofenac/placebo treatment group was demonstrated by capturing all both Q values and their corresponding q[L] values for the primary efficacy parameters shown as follows: Physician's Global: Mean Baseline- 0.97 [0.92, 1.03], Least Square Mean - 1.02 [0.96, 1.09]; Patient's Global: Mean Baseline - 0.98 [0.93, 1.03], Least Square Mean - 1.00 [0.94, 1.07].

Analysis of the secondary efficacy variables of ESR and Duration of Morning Stiffness showed that there were no significant differences between the 2 treatment groups at any of the evaluation time points.

Reviewer's Comments

The primary objective of this trial as stated in the protocol was to compare the gastroduodenal mucosal damage associated with the fixed combination of

diclofenac/misoprostol with that of the diclofenac/placebo combination. The determination of diclofenac/misoprostol's antirheumatic efficacy was a secondary objective which explains why the trial only studied 2 instead of 4 primary efficacy variables for rheumatoid arthritis as recommended by this reviewing division for NSAID class drug approval. It is therefore not surprising that the same comments about the trial design (non-flare, lacking a placebo-control arm), data analysis (i.e., the method used to calculate the Q statistic) and the interpretations of trial results apply here. The latter 2 areas as related to the trial's final outcome may have been negatively affected by the lack of stringent entry criteria for functional classification of rheumatoid arthritis. Thus patients with severe rheumatoid arthritis (i.e., class IV or wheelchair confined) may have been entered into this trial who were unable to demonstrate any treatment associated improvement of their arthritis during this trial. There is no way of knowing this since the Sponsor failed to collect this information at trial entry, and did not perform evaluations for joint tenderness and swelling. Therefore it is this medical reviewer's opinion that this trial be considered weakly supportive of the fixed combination diclofenac/misoprostol efficacy in the treatment of rheumatoid arthritis.

Section III - Miscellaneous Trials

PREVENTION OF CLINICALLY SIGNIFICANT DICLOFENAC-INDUCED GASTRODUODENAL MUCOSAL LESIONS BY MISOPROSTOL 200 MCG BID OR TID IN PATIENTS WITH RHEUMATOID ARTHRITIS OR OSTEOARTHRITIS.

Protocol EB2-87-02-269

Design:

This was a 52-week, multi-centered, double-blind, randomized, placebo-controlled trial of parallel group design conducted abroad to assess the efficacy of coadministered misoprostol 200 mcg with diclofenac 50 mg BID or TID in preventing clinically significant NSAID-induced gastroduodenal lesions and GI symptoms in NSAID intolerant patients with rheumatoid arthritis and osteoarthritis. As a secondary objective the trial assessed the clinical efficacy of coadministered misoprostol and diclofenac in the management of the signs and symptoms of the patients' arthritic conditions. Gastrointestinal evaluations via endoscopy and lab tests were performed at baseline and at Weeks 12, 24 and 52, while arthritis evaluations were conducted at baseline and Weeks 6,12, 18, 24, 36 and 52. Efficacy evaluations for both rheumatoid arthritis and osteoarthritis conditions were assessed via the following 6 efficacy parameters: Duration of Morning Stiffness, Duration of Immobility Before Joint Stiffness Recurs, Number of Nocturnal Awakenings Due to Arthritic Pain, Patient's Assessment of Arthritic Pain and a Global Assessment. Patients continued taking their previously prescribed NSAID during the pretreatment phase of this trial and were randomized to receive study medications after undergoing the baseline endoscopy.

Demographics and Disposition:

Of the three hundred eighty-four (384) patients enrolled in this trial, 192 carried a diagnosis of rheumatoid arthritis and 191 patients had a diagnosis of osteoarthritis. One patient with ankylosing spondylitis that had been entered into the trial was not included in the final arthritis assessment analysis. One hundred ninety-three (193) patients out of the 384 entered into this trial were randomized to the misoprostol/diclofenac treatment group versus 191 into the placebo/diclofenac treatment group. Thirty (30) out of the 193 patients from the misoprostol/diclofenac treatment group withdrew from the trial due to treatment failure as compared to 48 out of the 191 patients in the placebo/diclofenac treatment group. Treatment failure was defined as having endoscopically confirmed clinically significant gastroduodenal lesions. The Sponsor did not provide any information re: the numbers of patients who prematurely discontinued the trial due to lack of efficacy in terms of treatment of their underlying arthritic conditions.

Efficacy:

The following tables, Tables 25 and 26 (see below), list the P-values for the treatment comparisons of the ITT cohort analysis for the rheumatoid arthritis and the osteoarthritis populations. The Sponsor attributes the significant differences noted on comparison of the diclofenac/misoprostol versus the diclofenac/placebo treatment groups at the baseline (Week 0) evaluation for the Number of Times of Nocturnal Awakening Due to Arthritic Pain (p=0.0011) and the Patient's Assessment of Arthritic Pain (p=0.0170) in the rheumatoid arthritis patients due to the effects of continuing the patients' previous NSAID therapy. (Note: This trial did not have a washout period or built in "flare" requirement prior to randomization.) Significant differences were noted on comparison of the treatment groups in favor of the diclofenac/misoprostol group for the Week 6 evaluation for the Duration of Morning Stiffness (p=0.0170), Number of Times of Nocturnal Awakening Due to Arthritic Pain (p=0.0037), and Global Assessment (p=0.0140), and at the Week 52 evaluation for Patient's Assessment of Arthritic Pain (p=0.0240) for the rheumatoid arthritis patient population. For the osteoarthritis patients, the only statistically significant difference noted was in favor of the diclofenac/misoprostol group for the Number of Times of Nocturnal Awakening Due to Arthritic Pain (p=0.0179). (Refer to the following tables, Tables 25 and 26.) (See the HFD-150 medical officer's GI safety review for further discussion of this trial's data.)

Table 25- ITT Assessments From the Rheumatoid Arthritis Population of Study EB2-87-02-269

ASSESSMENTS OF RHEUMATOID ARTHRITIS
(Intent-to-Treat Cohort - Rheumatoid Arthritis)

	WEEK 0		WEEK 6		WEEK 12		WEEK 18		WEEK 24		WEEK 36		WEEK 52	
TREATMENT COMPARISONS:	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value
NO. OF JOINTS AFFECTED[a]	1.51	0.1303	1.18	0.2734	0.85	0.3945	1.73	0.0843	1.91	0.0555	0.78	0.4381	1.21	0.2245
DURATION OF MORNING STIFFNESS[a]	1.93	0.0538	2.39	0.0170*	0.20	0.8413	0.96	0.3390	1.29	0.1983	0.78	0.4380	0.90	0.3663
DURATION OF IMMOBILITY BEFORE JOINT STIFFNESS RECURS[a]	1.18	0.2373	0.28	0.8438	0.77	0.4424	0.46	0.6483	0.78	0.4371	0.65	0.5142	1.18	0.2390
OF TIMES OF URNAL AWAKENING TO ARTHRITIC N[a]	3.27	0.0011*	2.90	0.0037*	1.05	0.2946	0.72	0.4694	1.02	0.3093	0.91	0.3629	0.58	0.5623
PATIENT'S ASSESSMENT OF ARTHRITIC PAIN[a]	10.20	0.0170*	5.47	0.1400	2.82	0.4200	4.70	0.1950	4.83	0.3050	3.05	0.5490	9.42	0.0240*
GLOBAL ASSESSMENT[b]	5.33	0.1490	10.67	0.0140*	5.23	0.1560	3.78	0.2860	2.07	0.7220	3.94	0.2680	7.39	0.0610

[a] Mann-Whitney two-sample non-parametric test, where Z is the normal Z from the normal (uncorrected) approximation of the Mann-Whitney test.

[b] Chi-square calculated on 5 (max) x 2 table, including unknown category

* Statistically significant at the 5% level

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Table 26 - ITT Assessments From the Rheumatoid Arthritis Population of Study EB2-87-02-269

ASSESSMENTS OF OSTEOARTHRITIS
(Intent-to-Treat Cohort - Osteoarthritis)

	WEEK 0		WEEK 6		WEEK 12		WEEK 18		WEEK 24		WEEK 36		WEEK 52	
TREATMENT COMPARISONS:	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value	X^2	p-value
NO. OF JOINTS AFFECTED[a]	0.09	0.9318	0.50	0.6193	1.05	0.2915	0.48	0.6330	0.02	0.9835	0.21	0.8367	0.30	0.7670
DURATION OF MORNING STIFFNESS[a]	0.17	0.8658	0.48	0.6307	0.55	0.5792	0.10	0.9197	0.17	0.8627	0.15	0.8795	0.67	0.5036
DURATION OF IMMOBILITY BEFORE JOINT STIFFNESS RECURS[a]	0.89	0.3745	1.08	0.2790	0.63	0.5255	0.22	0.8264	0.81	0.4170	0.09	0.9320	0.12	0.9035
[illegible]F TIMES OF [illegible]NAL AWAKENING [illegible]O ARTHRITIC PAIN[a]	1.16	0.2463	2.37	0.0179*[1]	0.42	0.6738	0.42	0.6718	0.13	0.8974	1.83	0.0679	0.94	0.3468
PATIENT'S ASSESSMENT OF ARTHRITIC PAIN[a]	2.04	0.5650	5.16	0.2710	2.71	0.6080	3.84	0.2800	1.09	0.7790	5.98	0.1130	1.45	0.6950
GLOBAL ASSESSMENT[a]	7.50	0.0580	3.04	0.5520	3.41	0.4920	2.66	0.4480	1.24	0.7430	2.81	0.5910	1.75	0.6250

[a] Mann-Whitney two-sample non-parametric test, where Z is the normal Z from the normal (uncorrected) approximation of the Mann-Whitney test.

[b] Chi-square calculated on 5 (max) x 2 table, including unknown category

* Statistically significant at the 5% level

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Reviewer's Comments

This trial was designed primarily to assess the long-term efficacy (i.e., safety) of coadministered diclofenac and misoprostol in preventing the occurrence of NSAID-induced gastrotoxic lesions in arthritis patients with a history of NSAID intolerance. It was not designed to be a pivotal trial in demonstrating the anti-arthritic effectiveness of this coadministered combination as shown by the choice of efficacy parameters employed (Note: Besides not being the ones recommended for primary efficacy assessment for either disease, some of the parameters used in this trial are appropriate for evaluating one disease but not the other.), the lack of flare criteria or baseline washout period, the lack of a third treatment arm using a combination of placebo BID /TID with misoprostol, or in the "mixed" population of rheumatoid arthritis and osteoarthritis patients entered into the trial. It is a generally accepted practice that rheumatoid arthritis and osteoarthritis are studied separately when assessing a drug's antiarthritic effectiveness since they are two distinctly different disease entities with different therapeutic goals. In the treatment of rheumatoid arthritis the therapeutic goal is to decrease inflammation, whereas in osteoarthritis the goal is primarily aimed at analgesia. The proposed mechanism of action by which drugs from the nonsteroidal anti-inflammatory class exert their analgesic and anti-inflammatory effects has been shown to be dose related. Rheumatoid arthritis patients therefore tend to require higher doses of nonsteroidal anti-inflammatory drugs than patients with osteoarthritis. In this trial, the dose of diclofenac tested (150 mg a day in divided doses) represents the lower limit of the approved recommended dose range for diclofenac in the treatment of rheumatoid arthritis and the upper limit for the recommended dose range in the treatment of osteoarthritis. The clinical relevance of the findings from the arthritis assessment analysis of this trial are unclear to this reviewer. At best, this trial offers some supportive evidence of the product concept that diclofenac coadministered with misoprostol is an efficacious treatment of both rheumatoid arthritis and osteoarthritis.

A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF ADDING MISOPROSTOL TO DICLOFENAC ON RENAL FUNCTION AND ON THE PHARMACOKINETICS OF DICLOFENAC IN PATIENTS WITH RHEUMATOID ARTHRITIS AND MILD TO MODERATE RENAL IMPAIRMENT.

(Protocol EB2-87-02-272)

This trial was a 21-day, single site, double-blind, placebo-controlled crossover trial in 25 rheumatoid arthritis patients with mild to moderate renal insufficiency conducted in the Netherlands that assessed the pharmacokinetic profile of coadministered diclofenac and misoprostol and their affect on renal function. Patients were treated with diclofenac 50 mg TID for 14 days prior to undergoing renal evaluation.

Treatment with diclofenac 50 mg TID was maintained for the duration of the study including during the 10-day washout period between crossover treatments with either misoprostol or placebo. Renal function was monitored and assessed via 24-hour urine collections for creatinine clearance, urine volume, and urinary excretion of electrolytes, protein and glucose. Glomerular filtration and renal plasma flow were monitored via ^{125}I-thalamate and ^{131}I-hippurate infusion clearances. As part of the safety monitoring for this trial, a rheumatic assessment was performed comprised of the following 5 efficacy parameters: Joint Pain at Rest, Joint Pain on Movement, Fatigue, Overall Assessment and the Ritchie Index. The data collected from these assessments was presented by the Sponsor in summary format in Table 27 by treatment group. (See Table 27 below) This trial demonstrated that there was no apparent impact on efficacy observed for either coadministered misoprostol versus coadministered placebo. (Refer to the biopharmaceutical reviewer's NDA review for a full discussion of this trial's PK findings.)

Table 27 - Table of Rheumatological Assessment By Treatment for Subjects with All Measurements in Study EB2-87-02-272

		Diclofenac/ MISOPROSTOL (N=24)		Diclofenac/ PLACEBO (N=24)	
		PRE	POST	PRE	POST
JOINT PAIN AT REST	None	12	10	14	14
	Mild	6	4	3	5
	Moderate	5	9	5	3
	Severe	1	1	2	2
JOINT PAIN ON MOVEMENT	None	5	5	2	3
	Mild	8	6	6	4
	Moderate	8	12	13	14
	Severe	3	1	3	3
FATIGUE	None	10	12	12	8
	Mild	4	4	5	3
	Moderate	9	7	3	9
	Severe	1	1	4	4
OVERALL ASSESSMENT	Good	9	6	6	6
	Average	14	15	14	14
	Bad	1	3	4	4
RITCHIE INDEX - ADJUSTED TOTAL SCORE (a)	Median	11	11	13	11
	Range	0-38	0-38	2-32	1-35

NOTE : (a) When number of joints measured was less than twenty five the score was adjusted using (total score x 25)/(number of joints)

Reviewer's Comments

This trial offers little support of the product concept that short-term coadministration of misoprostol with diclofenac does not affect the therapeutic effectiveness of diclofenac in rheumatoid arthritis due to the trial's short duration, small sample size and the choice of arthritis efficacy parameters studied. This claim is weakened further by the use of a formulation different from the one the Sponsor proposes to market.

Medical Reviewer's Summary

Review of the data from the 4 osteoarthritis trials (Studies NN2-94-02-349, IN2-89-02-298, IN2-89-296 and IN2-90-02-321) supplied by the Sponsor in support of the indication of osteoarthritis provides sufficient evidence that Arthrotec I given three times a day (TID) and Arthrotec II given twice daily (BID) are efficacious in the treatment of osteoarthritis. The strongest evidence for an OA claim was provided by Study NN2-94-02-349, a randomized, double-blind, placebo-controlled trial in which both Arthrotec I and II were shown to be comparable to the active comparator, diclofenac, on 3 out of 3 primary efficacy variables. Treatment with the formulation of diclofenac used in this trial was also shown to be statistically more effective than placebo on 2 out of 3 primary efficacy variables. On secondary pairwise comparisons, both Arthrotec I and II were shown to be significantly more effective than placebo. Studies IN2-89-02-298 and IN2-89-296 which were randomized, double-blind, active-controlled trials that essentially utilized the same protocol except that the patients in the latter trial also underwent endoscopic examination, provided evidence for comparability between diclofenac and Arthrotec I on 3 out of 3 primary efficacy variables. It should be noted that the support provided for an OA claim by these 2 trials is not as strong as Study NN2-94-02-349 due to various problems related with trial design (i.e., non-flare, lacking a placebo-control arm and unfixed dose regimens). The forth trial submitted in support of an OA claim, Study IN2-90-02-321, was another randomized, double-blind, active comparator trial in which Arthrotec I was found to be comparable to the 2 active comparators, naproxen and piroxicam, on 3 out of 3 primary efficacy variables. Although this trial also lacked a placebo-control arm, it does show that Arthrotec I is an equivalent treatment for OA as compared to 2 other approved NSAIDs.

The data from the 3 rheumatoid arthritis trials (Studies NN2-95-ST-352, IN2-89-02-292, and IN2-89-02-289) and the 2 miscellaneous trials (Studies EB2-87-02-269 and EB2-87-02-272) failed to provide sufficient conclusive evidence that either Arthrotec I or II were efficacious agents in the treatment of rheumatoid arthritis. The major problem with the rheumatoid arthritis portion of this NDA application is related to the failure of the diclofenac formulation used as the active comparator in Study NN2-95-ST-352 to be statistically better than placebo in the treatment of this condition. In this randomized,

double-blind, placebo-controlled trial, the diclofenac formulation used as the active comparator was unable to beat placebo on 4 out of 4 primary efficacy variables at the Week 6 time point, but was shown to be statistically better than placebo on 2 out of 4 primary efficacy variables. While both Arthrotec I and II were comparable to diclofenac on all 4 primary efficacy variables on the principle pairwise comparisons, Arthrotec II was also shown to beat placebo on 3 out of 4 efficacy parameters at Week 6, but only 2 out of 4 parameters at Week 12. Arthrotec I failed to beat placebo on any of the primary variables at the Week 6 time point and was shown to be statistically superior as compared to placebo at the Week 12 time point for only 1 out of 4 efficacy parameters. For a rheumatoid arthritis efficacy claim, an NSAID is considered to be effective if at least 3 out of the 4 primary efficacy variables are statistically significantly better than placebo. With the failure to validate the active comparator (diclofenac) used in this trial which was one of the study's stated primary objectives, the relevance of Arthrotec II's superiority to placebo is highly questionable since it and Arthrotec I were both shown to be equivalent to diclofenac.

The 2 other rheumatoid arthritis trials reviewed for this NDA submission, Studies IN2-89-02-292 and IN2-89-02-289, were randomized, double-blind, non-placebo controlled trials that compared Arthrotec I versus diclofenac. In the first trial, Study IN2-89-02-292, patients were required to have been on a stable dose of diclofenac prior to trial entry but were not required to undergo a washout period prior to randomization. In addition, the doses of study medication were not fixed. At best this trial offers supportive evidence that treatment with Arthrotec I was comparable to that with diclofenac in "maintaining" a therapeutic response to diclofenac. Study IN2-89-02-289, was also a non-flare trial, and only used 2 instead of 4 primary efficacy variables to assess patients' response to treatment with study medications as recommended by this reviewing division for NSAID class drug approval. It therefore can only be considered supportive for a rheumatoid arthritis claim. The miscellaneous trials (Studies EB2-87-02-269 and EB2-87-02-272) only offer supportive evidence of the product concept that diclofenac coadministered with misoprostol is an efficacious treatment of rheumatoid arthritis. Based on the data reviewed in this submission, a rheumatoid arthritis indication for this NDA application could only be approved if there was sufficient evidence noted by the pharmacokinetics reviewer of the PK data in this submission to satisfy the Division of Biopharmaceutics criteria for a bioequivalency claim between the formulation of diclofenac used as the active comparator in the aforementioned trial, and a diclofenac formulation currently approved for marketing in the U.S.

This formulation may or may not be indicated for pediatric usage due to the abortifacient potential of the misoprostol component. The originator of diclofenac sodium did not seek an indication for pediatric usage, nor is this Sponsor presently seeking one. Keeping in mind the FDA's pediatric directive, consideration should be given to performing a PK trial in children as a Phase IV commitment if and when this NDA application is approved. If the Sponsor decides to further pursue a rheumatoid arthritis claim for this product, there should be some consideration for a trial using the Arthrotec equivalent of 200 mg a day in divided doses in this population for both

efficacy and safety reasons.

/S/

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Rosemarie Neuner, MD, MPH

12-6-96

cc: orig NDA
HFD-550/Div. File
HFD-180
HFD-550/MO/Neuner
HFD-550/MO Team Leader/Hyde
HFD-550/Act Div Dir/Chambers

/S/

See Division Director's Memorandum
/S/ 12/9/96

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

NDA:	20-607 MAR - 7 1997
Document Identification:	AM
Sponsor:	G. D. Searle & Co.
Drug name:	Arthrotec (diclofenac sodium/misoprostol) 50mg/200mcg and 75mg/200mcg Tablets
Date submitted:	December 17, 1996
Date received:	December 18, 1996
Review completed:	February 28, 1997
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
The sponsor has applied for approval to market two fixed combination products, Arthrotec 50 (diclofenac sodium 50mg/misoprostol 200mcg) and Arthrotec 75 (diclofenac sodium 75mg/misoprostol 200mcg), for acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk for developing non-steroidal anti-inflammatory drug-induced (NSAID-induced) gastroduodenal ulcers. The diclofenac sodium component would provide the antiarthritic efficacy and the misoprostol component would provide gastric and duodenal mucosal protection. The proposed dose for Arthrotec 50 in both osteoarthritis and rheumatoid arthritis is one tablet two or three times per day (providing 100-150 mg diclofenac and 400-600mcg misoprostol daily); the proposed dose for Arthrotec 75 is one tablet two times per day (providing 150mg diclofenac and 400mcg misoprostol daily).

In my Medical Officer's review dated 12/5/96 of the original NDA 20-607 submission, I reviewed clinical studies submitted in support of efficacy of Arthrotec 50 and Arthrotec 75.

- For Arthrotec 50, I concluded that no studies in the application could be applied to demonstrate effectiveness of the Arthrotec 50 formulation proposed for marketing because that formulation was not studied in clinical trials <u>and</u> the formulations studied were not shown to be bioequivalent to the product intended for marketing. It was recommended that the sponsor establish bioequivalence between the Arthrotec 50 formulation proposed for marketing and marketed Cytotec + Voltaren through a direct comparison bioequivalence study. If such bioequivalence were to be demonstrated, the clinical efficacy information supporting labeling of Cytotec for prevention of NSAID-induced gastric and duodenal ulcers would then be applicable to Arthrotec 50.

- For Arthrotec 75, I concluded that the sponsor had one adequate and well-controlled clinical trial (Study 349, a 6-week study done in osteoarthritis patients) supporting effectiveness of Arthrotec 75 given BID 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 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. It was recommended that the sponsor 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 then be applicable to Arthrotec 75.

In the current submission the sponsor amends the original NDA for Arthrotec to include the report for an additional clinical study, Study I88-94-02-013 (Study 013). This study is incorporated by reference ; for Arthrotec to which the report for Study 013 was submitted on 9/17/96.

. The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) is reviewing this submission with regard to anti-arthritic efficacy.

Reviewer's Comments and Discussion:
Study 013 was a 12-week, randomized, multicenter, "double-blind" trial in 514 patients with osteoarthritis or rheumatoid arthritis comparing the antiarthritic efficacy and gastroduodenal safety of Arthrotec 75 with that of a sustained release formulation of diclofenac sodium. The Arthrotec 75 formulation used was the formulation the sponsor intends to market. The sustained release diclofenac sodium formulation

With regard to evaluation of efficacy in preventing gastric and duodenal ulcers, Study 013 was not well-designed or executed. Major deficiencies included the following:

1. No "baseline" endoscopy was done to document lack of ulcers in patients at study entry. Endoscopy was done only at completion of treatment with study drug.

2. Blinding of the study may have been compromised by the fact that the appearance of the Arthrotec tablets was different from that of the sustained-release diclofenac sodium tablet.

3. No bioequivalence information was provided to link the sustained release diclofenac sodium formulation used in Study 013 to any diclofenac sodium product approved for marketing in the U.S.

Statistical comparison between groups for the prevalence of ulcers at study completion suggested that gastric ulcers were more frequent in the sustained release diclofenac group as compared to the Arthrotec 75 group (12.3% vs. 4.3%, p=0.001). However, the lack of knowledge of the baseline status of the patients, makes it impossible to draw any reliable conclusion from the ulcer data. For duodenal ulcer, the prevalence at study completion was 5.4% in the sustained release diclofenac patients and 1.6% in the Arthrotec 75 patients (p=0.028). It should be noted that in each treatment group about 13% of enrolled patients did not undergo the endoscopy specified in the protocol. Thus, the robustness of the result is further compromised by a problem of missing data.

Conclusions and Recommendations:

In conclusion, Study 013 is not an adequate and well-controlled study of Arthrotec 75 for prevention of NSAID-induced upper gastrointestinal ulceration.

The recommendations remain the same as in my review of NDA 20607 dated 12/5/96.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 3/7/97

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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-550
HFD-870/H-RChoi
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APPENDIX 1

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FEB 28 1997

Medical Officer's Review of Request for Consultation (HFD-180)

NDA 20-607

Submitted date (HFD-550): January 6, 1997
Submitted date (reviewer): January 7, 1997
Review completed: February 14, 1997

Sponsor: G.D. Searle
4901 Searle Parkway
Skokie, Ill. 60077

Drug: Arthrotec (diclofenac sodium/misoprostol)

Pharmacologic Category: anti-inflammatory

Dosage form: tablet

Route of Administration: oral

Submitted: Clinical study entitled "Report of a randomised, blinded three-month study in patients with rheumatoid arthritis or osteoarthritis, in which diclofenac 75 mg slow release and the combination tablet, diclofenac sodium 75 mg/misoprostol 200 μg (Arthrotec 75), both administered twice a day, were compared for antiarthritic efficacy, tolerability and incidence of endoscopically detected upper GI damage. Protocol I88-94-02-013, Report I88-96-06-013."

Background:
Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) which has been approved since 1988 for the treatment of the acute and chronic symptoms associated with rheumatoid arthritis (RA; doses range 150-200 mg/day in divided doses), osteoarthritis (OA; doses range from 100-150 mg/day in divided doses) and ankylosing sypondylitis. Misoprostol is a synthetic prostaglandin E_1 analogue that has been approved for the prevention of NSAID-induced gastric ulceration in patients at high risk for such ulcers. ***This consult will not deal with the issues involving efficacy and safety of gastrointestinal endpoints in this protocol but will focus on the evaluation of claims aimed at the efficacy and safety in RA and OA.***

The original Arthrotec was a combination of diclofenac 50 mg/misoprostol 200 μg and is now licensed in Canada, Germany, Holland, Portugal, Sweden and the UK. Literature studies, involving over 3,000 patients with either RA or OA, have claimed efficacy comparable (or superior) to diclofenac (not slow release formulation) and other NSAIDs (naproxen, piroxicam,

indomethacin, ibuprofen) at BID or TID dosing. These same studies are also reported to show that Arthrotec was associated with a significantly lower incidence of gastroduodenal ulcers. The development of Arthrotec 75 (diclofenac 75 mg/misoprostol 200 mcg) was prompted by the observation that the higher doses of diclofenac may be needed to control the signs and symptoms of approximately 70% of patients with RA and 40% of patients with OA. The Arthrotec 75 tablet is, therefore, designed to deliver 150 mg of diclofenac on a BID dosing regimen without increasing the amount of misoprostol.

Objective/Rationale:
The **primary objectives** were to assess the anti-arthritic efficacy (i.e. control the signs and symptoms) and gastroduodenal mucosal damage (as assessed by endoscopy) of Arthrotec 75 vs diclofenac 75 mg (slow release formulation) in patients with RA and OA. If patients were already receiving a NSAID, there had to be a reason to change which could include an expectation of improvement in either efficacy or tolerability. There is, apparently, little published information available on the gastrointestinal (GI) safety of the slow release form of diclofenac. **Secondary objectives** were to compare the tolerability of these two treatments in terms of withdrawals for adverse events, overall incidence of adverse events and effects on hemoglobin concentration, serum ALT and creatinine. **This study, therefore, represents the first comparison of Arthrotec 75 and diclofenac 75 mg slow release.** It is also noted that the endoscopy only at the end of the study would mimic clinical practice since a proportion of the patients would probably have had pre-existing ulceration but were not excluded from the study (i.e. "all comers" were included).

Protocol Design:
This was a multicenter, multinational (51 investigators in 10 countries; Belgium, Canada, France, Germany, Holland, Norway, South Africa, Sweden, Switzerland, UK), randomized, blinded, 2-arm parallel comparison of Arthrotec 75 versus diclofenac 75 mg slow release (Voltarol, except for dosage strength of diclofenac, this is the same formulation as Voltaren XR 100 mg; NDA 20-254) BID for 12 weeks. **Patients were not flared.** Assessments of arthritic efficacy and laboratory tests were performed at baseline and after 4, 8 and 12 weeks of treatment while a single endoscopy was performed only at final follow-up (week 12) or when the patient withdrew from the study if this occurred earlier. Blood samples were collected at each visit for clinical laboratories (creatinine, ALT, hemoglobin) and analyzed either centrally (London) or at a local laboratory. Blood samples were also taken to assess *H. pylori* status.

There were **three protocol** (study dates were from November 29, 1994 to February 5, 1995) **amendments.** Amendment 3 (October 6, 1994), which applied to all sites, clarified that analgesics (e.g. paracetamol) were not to be used 48 hours before arthritic assessments; if used daily the patient was to be excluded from the study (and listed as a treatment failure) but if analgesic use was 'prn' the average daily consumption was recorded.

Blinding (since the tablets were not identical in appearance) was achieved by foil/foil packing of the drug supplies and counting of unused medication by a third party. The use of other NSAIDs (including topical NSAIDs) or antiulcer drugs was excluded; there were no restrictions on second-line arthritis medications.

Endpoints of anti-arthritic efficacy included:

primary: -physician and patient globals on a 5-point categorical scale (very good, good, fair, poor, very poor)

secondary: -night pain (previous 3 nights, 4-point scale)
-duration of morning stiffness (previous 3 days)
-health assessment questionnaire for RA only (modified by Kirwan to assess disability in British patients with RA; Br. J. Rheumatol 25:206, 1986)
-osteoarthritis severity index (OSI) for OA only (Lequesne; Scand J Rheumatol Suppl 65:85, 1987). This composite index which consists of 3 patient self-assessments including severity of OA pain, walking distance and activities of daily living has a maximum score of 24.

treatment failures: patients withdrawing from the study because of worsening of their arthritic condition

NSAID therapy no longer required: those withdrawing because their condition improved to such an extent that NSAID therapy was no longer required.

For all arthritis assessments, endoscopy data and for all data relating to withdrawals and serious adverse events, there was apparently a 100% audit of the original CFR performed by the sponsor.

Population

Patients that were aged 18 years or older qualified for the study if they had a diagnosis of RA (ARA criteria) or OA of the hip or knee (ACR criteria) for at least 6 months with a functional capacity classification of I-III and required NSAIDs. Patients **excluded** were those with **known or suspected active peptic ulceration or gastrointestinal bleeding,** clinically significant renal or hepatic dysfunction, Crohn's disease, ulcerative colitis or any other condition which might preclude the use of NSAIDs. Also, patients who were anticipated to require treatment with any NSAID or **antiulcer drug**, other than study medication, were excluded. All patients gave written, informed consent prior to participating in this study.

Statistical considerations:

A separate randomization schedule was employed for patients with RA and OA with subject numbers 0001-1000 for RA and 1001-2000 to OA. Patients were randomized in blocks of six for each center. There were 6 patients (1.2%) lost to follow-up and a further 24 patients were withdrawn for a pre-existing violation of entry criteria or protocol non-compliance. These losses were equally distributed and so the total randomized were included as the denominators for the ITT analysis of efficacy assessments and adverse events profiles.

Power calculations were carried out for the two primary response variables i.e. the gastroduodenal ulceration rate and the global assessments of arthritis in general practice. Regarding the latter, a previous study assessing globals at four months suggested that a sample size of 200 per treatment group provided 80% power to detect a difference between 50% on

one treatment arm and 35.8% (or 64.2%) on the other using a two-sided test at the 5% level of significance.

The full ITT cohort was used for analysis without excluding those who took no medication or who were found to be ineligible after admission since there were only 3 such patients in each group. **Missing data** for assessments of arthritis for patients who cited treatment failure as their reason for withdrawal were **imputed** by carrying forward their last know globals and night pain. These patients were **NOT** assigned the worst possible score because some deteriorated by only one grade (e.g. 'very good' to 'good') and withdrew and so it was felt that categorization to the worst score overestimated this deterioration.

At baseline, a greater percentage of patients (especially with RA) had a physician's global assessment of "**very good**" in the diclofenac vs Arthrotec 75 group (i.e. 7.1% vs 0.7%, respectively). This imbalance made it necessary to evaluate the efficacy assessments (globals and night pain) according to percentage change (improvement or worsening) from baseline rather than by comparison of the absolute scores at each follow-up visit. Nonetheless, this still gave rise to categorical data which were analyzed by logistic regression.

Morning stiffness data was also reduced to categorical data and analyzed by logistic regression while age, sex, site, country, duration of treatment, tablet consumption and concomitant medication were included as potential covariates in the efficacy assessments.

Survival analyses using time to withdrawal were used to compare the tolerability of the two drugs. Adverse events with a frequency of more than 2% of patients on either treatment were compared using Fisher's exact test.

Results:

The demographics and baseline data of patients entered into this study are noted in the following first four tables (in ALL the tables, percentages are rounded to the nearest whole number unless otherwise indicated).

Table 1: Demographics of Intent-to-Treat Group (%)

	Arthrotec 75	Diclofenac 75 SR	Overall
Total patients	253 (100)	261 (100)	514 (100)*
OA total	107 (42)	106 (41)	213 (41)
RA total	146 (58)	155 (59)	301 (59)
Age (mean)	59	60	
Sex (% female)	(69)	(69)	
OA hip (left/right/either)	20/20/32	19/16/26	39/36 58
OA knee (left/right/either)	65/72/87	58/71/89	123/143/176
OA duration (yrs)	6.7	7.0	6.9

* 3 patients had a diagnosis of OA and RA; these were excluded from OA patient numbers

Reviewer's comment: Randomization appears to have matched the two treatment groups in terms of baseline characteristics such as gender, age, as well as type, duration and location (OA) of arthritis. Demographics on race were not included. There is no target joint identified in the OA population.

Table 2 presents the results of the number of patients with either RA or OA who were taking either diclofenac alone, Arthrotec (presumably the 50 mg diclofenac formulation), or misoprostol along with some other NSAID.

Table 2: Prestudy NSAIDs in OA/RA Patients			
	Arthrotec 75	Diclofenac 75 SR	Overall
None	73	70	143
Diclofenac alone	78	76	154
Diclo/misoprostol*	16	11	27

* This refers to Arthrotec combination tablet, a few patients (not listed here) were also taking misoprostol separately with another NSAID. This table is reviewer generated.

Reviewer's comment: While randomization may have balanced patients with regards to prior use of NSAIDs, it is unclear why any patients were receiving diclofenac (with or without misoprostol) since there needed to be a reason to switch (see objective/rationale section above).

Table 3, which follows, presents the baseline physician global assessments at baseline for both OA and RA. Patients were assessed on a 5-point categorical scale.

Table 3: Physician's Global Assessment - Baseline (%)				
	OA		RA	
	Arthrotec 75	Diclofenac 75 SR	Arthrotec 75	Diclofenac 75 SR
Very Good	3 (3)	2 (2)	1 (1)	11 (7)
Good	33 (32)	28 (27)	45 (32)	47 (31)
Fair	51 (49)	56 (55)	73 (51)	75 (48)
Poor	15 (15)	16 (16)	20 (14)	20 (13)
Very Poor	1 (1)	0	3 (2)	1 (1)
Total	103 (100)	102 (100)	142 (100)	154 (100)

Reviewer's comment: The discrepancy of RA patients classified as "very good" has been discussed above in the statistical section. However, overall the patients appear to be balanced in terms of this baseline global assessment.

Table 4 below presents the patient's global score at baseline for both OA and RA. Once again, patients were assessed on a 5-point categorical scale.

Table 4: Patient's Global Score- Baseline (%)				
	OA		RA	
	Arthrotec 75	Diclofenac 75 SR	Arthrotec	Diclofenac 75 SR
Very Good	5 (5)	3 (3)	4 (3)	10 (7)
Good	29 (27)	29 (27)	37 (25)	42 (27)
Fair	49 (45)	47 (44)	74 (51)	74 (47)
Poor	20 (19)	25 (24)	25 (17)	25 (16)
Very Poor	4 (4)	2 (2)	6 (4)	4 (3)
Total	107 (100)	106 (100)	146 (100)	155 (100)

Reviewer's comment: Once again, the patients appear to be balanced at baseline with respect to patient's global assessment at baseline.

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Table 5 shows the results of patient disposition in this protocol. These results are given both in terms of all patients and the contributions from patients with either OA or RA separately.

Table 5: Reasons for Ending Study Participation by Arthritis Type (OA/RA)			
	Arthrotec 75	Diclofenac 75 SR	Overall
Total patients	253 (107/146)	261 (106/155)	514 (213/301)
Completed	177 (75/102)	184 (79/105)	361 (154/207)
Lost to follow-up	2 (1/1)	4 (4/0)	6 (5/1)
Withdrew (total)	74 (31/43)	73 (23/50)	147 (54/93)
pre-existing violation of entry criteria	1 (1/0)	2 (0/2)	3 (1/2)
protocol non-compliance	12 (5/7)	9 (4/5)	21 (9/12)
treatment failure	8 (3/5)	7 (0/7)	15 (3/12)
adverse event	53 (22/31)	55 (19/36)	108 (41/67)

Reviewer's comment: Looking at the two treatment groups, they appear balanced with regard to numbers and reasons for ending participation in this study. However, it should be noted that the fixed dose of diclofenac in Arthrotec as given in this study (i.e. 150 mg) is at the high end of the approved indication for OA but at the lower end for RA; this difference is reflected in the fact that the treatment failures were mostly from the RA group. The adverse events withdrawals were mainly associated with GI events (see table 9 in the safety section).

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Table 6 shows the results in the **a primary outcome variable** which is the change in global assessments by the physician for patients on either Arthrotec or diclofenac at final follow-up.

Table 6: Changes from baseline in Physician's Global Assessment with known outcomes at Final Follow-up			
	Arthrotec 75	**Diclofenac 75 SR**	**p-value**
	%	%	
OA (total)[1]	100 (n=103)	100 (n=104)	0.537
improved ≥ 2 grades	13.6	13.5	
improved by 1 grade	29.1	31.7	
no change	35.9	38.5	
worsened by 1 grade	16.5	13.5	
worsened ≥ 2 grades	4.9	2.9	
RA (total)[2]	100 (n=142)	100 (n=154)	0.139
improved ≥ 2 grades	11.3	8.6	
improved by 2 grades	27.5	25.0	
no change	45.8	44.1	
worsened by 1 grade	13.4	17.1	
worsened ≥ 2 grades	2.1	5.3	

[1] For Arthrotec includes 103, 90 and 83 patients at first/final, second and third visit, respectively. For diclofenac includes 102 (104), 86 and 82 patients at first (final), second and third visit, respectively. There were 213 patients in the ITT group.

[2] For Arthrotec includes 142, 119 and 109 patients at first/final, second and third visit, respectively. For diclofenac includes 154, 127 and 114 patients at first/final, second and third visit, respectively. There were 301 patients in the ITT group.

Reviewer's comment: There appears to be no clinically or statistically significant differences between Arthrotec and diclofenac in either disease with respect to the physician's global assessment. The greatest percentage of patients in either the RA or OA groups are in the 'no change' category.

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Table 7 which follows presents the other primary outcome variable which is change from baseline in the patient's global assessment at final follow-up.

Table 7: Changes from baseline in Patient's Global Assessment with known outcomes at Final Follow-up			
	Arthrotec 75	Diclofenac 75 SR	p-value
	%	%	
OA (total) [1]	100 (n=103)	100 (n=104)	0.690
improved ≥ 2 grades	19.4	17.3	
improved by 1 grade	20.4	25.0	
no change	39.8	40.4	
worsened by 1 grade	12.6	12.5	
worsened ≥ 2 grades	7.8	4.8	
RA (total)[2]	100 (n=143)	100 (n=152)	0.952
improved ≥ 2 grades	11.2	11.2	
improved by 1 grade	24.5	27.0	
no change	44.8	39.5	
worsened by 1 grade	12.6	15.1	
worsened ≥ 2 grades	7.0	7.2	

[1] See footnote 1 of table 5.

[2] For Arthrotec includes 143, 120 and 109 patients at first/final, second and third visit, respectively. For diclofenac includes 154 (152), 127 and 114 patients at first (final), second and third visit, respectively.

Reviewer's comment: There appears to be no clinically or statistically significant differences between Arthrotec and diclofenac in either disease with respect to patient's global assessments. Once again, the greatest percentage of patients are in the 'no change' category for either OA or RA.

The **secondary endpoints** comparing Arthrotec and diclofenac are shown separately for OA or RA in table 8 below. The values tabulated are the percentage change from baseline value as noted at the final follow-up.

Table 8: Percent changes from baseline for secondary outcomes at final follow-up					
		RA		OA	
		Arthrotec	Diclofenac	Arthrotec	Diclofenac
Night pain	improved	29	36	36	41
	none	55	47	54	53
	worsened	16	17	10	6
	(p-value)	0.286		0.233	
OSI*	improved			32	40
	none			54	48
	worsened			14	12
	(p-value)			0.187	
HAQ*	improved	19	24		
	none	63	63		
	worsened	18	13		
	(p-value)	0.790			

* OAI = Osteoarthritis Severity Index; HAQ = Health Assessment Questionnaire

Reviewer's comment: None of these secondary outcomes seems to have been different clinically or statistically for Arthrotec or diclofenac 75 SR.

Safety Results:

There were no deaths noted in this study. One patient (patient 298, BE 0010) with RA developed a perforated peptic ulcer requiring hospitalization while on diclofenac 75 SR. Table 9 lists withdrawals that were associated with treatment emergent signs and symptoms that occurred at a rate of 1% or greater.

Table 9: Withdrawals associated with treatment emergent signs and symptoms (≥ 1%)

	Total	Arthrotec 75 (n=253)			Diclofenac 75 SR (n=261)		
WHO term		No.	%	% severe	No.	%	% severe
Abdominal pain	48	21	8	15*	27	10	18*
Nausea	30	17	7	6	13	5	11
Diarrhea	20	9	4	9	11	4	20
Vomiting	17	10	4	26	7	3	24
Dyspepsia	10	6	2	8	4	2	18
Flatulence	6	3	1	6	3	1	0
SGPT increased	5	3	1	-	2	1	-
Vaginal hemorrhage	2	2#	1	-	0	0	-
Other ADEs (≤ 1%)	50	24	NA	-	26	NA	-
Total (withdrawing for ADE)	108	53	20.9	-	55	20.3	-

NA= not applicable since sponsor notes ADEs are not mutually exclusive and cannot simply be added one to another. # : only applies to female patients and total denominator = 174.
* symptoms severity (mild, moderate, severe) of adverse events.

> **Reviewer's comment:** Adverse events were only those offered spontaneously by the patients. As can be seen, GI events dominated with suggestions of some differences in the reporting of the severity of symptoms. The vaginal bleeding has been noted in other female patients taking misoprostol and is included in its labeling.

Summary/Discussion:

Efficacy

The main reason to want to combine a classic NSAID like diclofenac with the GI effects of misoprostol centers around the decision by the physician that misoprostol should be given to the patient (i.e. they are at risk from NSAID induced ulceration). The combination drug Arthrotec should improve compliance (i.e. less medicine to take) provided there are no contraindications to diclofenac. If it is agreed that the patient most likely to get into trouble with NSAID induced GI ulceration is the "elderly female", then this protocol seems to generally study those kinds of patients (Table 1) although the mean ages could be higher.

The exact purpose of this trial is unclear. It is stated that there will be a "comparison" of Arthrotec (in the 75 mg diclofenac versus the original 50 mg diclofenac combination, i.e. Arthrotec II versus Arthrotec I) and diclofenac (in the SR versus IR formulation) and so this is

assumed to be an equivalency trial. Such trials, as has been pointed out numerous times by others, tend to obfuscate issues and reward poor trial design and conduct. This protocol seems to follow that pattern.

For example, the sponsor notes that in patients already receiving a NSAID, there 'had to be a reason to change which could include an expectation of improvement in either efficacy or tolerability'. As noted in Table 2, roughly one-third of patients entered into this trial were taking either diclofenac with or without misoprostol. It could well be expected that these "selected" patients would show "no change" in either efficacy or tolerability. The sponsor also notes that this study extended the results of previous trials showing efficacy of misoprostol with a reduction in gastroduodenal ulceration in a more 'real-life' setting. Virtually no "real" patients undergo an endoscopy at a preset time after starting a therapy; patients have endoscopy for cause. Consequently, the entry criteria for this trial could have excluded patients already receiving one of the study drugs and included a baseline endoscopy.

The type of information provided in tables 3, 4, 6, & 7 represent what typically has been presented in NSAID trials in OA and RA as a **primary outcome variable**. While patient and physician globals are certainly important to evaluating a drug, others argue they only address part of the story. The tender and swollen joint counts, especially in RA, may well be a stronger representation of what is clinically relevant which helps to explain why these variables are **REQUIRED** outcomes variables in the ACR 20 responder index (ACR 20: ≥ 20% improvement in tender and swollen joint count + ≥ 20% improvement in 3 of 5 to include patient and physician globals, patient pain assessment, patient self assessed disability, and ESR/CRP) that is currently being considered as a sufficient composite endpoint in clinical trials to allow a label claim to mitigate the "signs and symptoms" in the current draft RA guidelines. The "traditional" FDA primary efficacy endpoints for RA also include the globals along with tender and swollen joint counts (need to "win" on 3 of these 4).

Of the **secondary outcome variables** of night pain (both RA and OA), Osteoarthritis Severity Index (obviously only in OA) and the HAQ (only in RA), it could be argued that the OSI represents the other primary efficacy variable (besides the globals) of joint pain generally sought in OA trials. However, as noted in table 1, there is no "target joint" identified in this protocol and so any relief of joint pain may come from different joints at different visits. Similarly, the HAQ is one of the optional components of the ACR 20 index (see above) and so could be argued to be evidence in support of the globals in the RA patients but the HAQ has not generally stood alone as a primary outcome in NSAID trials. Night pain is considered to be too variable to be of help as an outcome measure. There was no comment made on analgesic use and there were no patients that discontinued NSAID use because it was no longer required.

Therefore, without the inclusion of the primary endpoints of swollen and tender joint counts and without a placebo or a flare design (a flare design has traditionally allowed calculation of the Q-value which has been utilized to estimate differences in NSAID trials); it is difficult to make accurate conclusions about the efficacy of Arthrotec in patients with either OA or RA.

Therefore, the following statements apply to this protocol:

- Lack of statistically significant differences in not evidence of equivalence
- Lack of a flare means one can not do the usual Q analysis to assess equivalence
- Lack of "traditional disease specific" endpoints such as tender and swollen joint counts in RA or target joints in OA, would have made it hard to claim substantial evidence even if the study did have a flare and appropriate analysis

Safety

Adverse events (Table 9) were only those offered spontaneously by the patients and there are no surprises in the sense that GI complaints dominated. The trade-offs in the complex of GI symptoms between the two treatments as noted by the sponsor (i.e. more abdominal pain alone or in combination with dyspepsia in patients receiving diclofenac versus the reflux/bloating type symptoms of nausea, dyspepsia and flatulence with Arthrotec) is interesting but probably of questionable clinical value. Other adverse events, such as the vaginal bleeding has been noted in patients taking misoprostol and is included in its labeling. There were no deaths in this study. Of note in the listing of treatment emergent signs and symptoms that occurred with an incidence of ≥ 2% (not included) is the apparent increase in nausea in the Arthrotec group but the similarity in percentages of patients with diarrhea and SGPT increases; the latter data when analyzed by *de novo* elevations is used by the sponsor to argue for a potential hepatoprotective effect of misoprostol.

Conclusions:

This trial was submitted to support the claim of efficacy and tolerability of Arthrotec 75 as compared to diclofenac 75 mg SR in patients with RA and OA. The information included in this protocol suggests that although the two treatments seemed to perform similarly, the study doesn't provide substantial evidence for efficacy in RA, and probably not in OA.

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/S/

(James Witter, M.D., Ph.D. Medical Officer)

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cc: Orig NDA 20-607
HFD-180
HFD-550
HFD-550/MO/Witter
HFD-550/PM/Lobianco
/S/ 2/21/97

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

NDA:	20-607
Document Identification:	N
Sponsor:	G. D. Searle & Co.
Drug name:	Arthrotec Tablets (diclofenac sodium /misoprostol)
Date submitted:	December 22, 1995
Date received:	December 26, 1995
Review completed:	November 14, 1996
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Dec. 5, 1996
/S/

In this submission the sponsor proposes marketing two fixed combination products, Arthrotec 50 (diclofenac sodium 50mg/misoprostol 200mcg) and Arthrotec 75 (diclofenac sodium 75mg/misoprostol 200mcg), for acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk for developing non-steroidal anti-inflammatory drug-induced (NSAID-induced) gastroduodenal ulcers. The diclofenac sodium component would provide the antiarthritic efficacy and the misoprostol component would provide gastric and duodenal mucosal protection. The proposed dose for Arthrotec 50 in both osteoarthritis and rheumatoid arthritis is one tablet two or three times per day (providing 100-150 mg diclofenac and 400-600mcg misoprostol daily); the proposed dose for Arthrotec 75 is one tablet two times per day (providing 150mg diclofenac and 400mcg misoprostol daily). A copy of the sponsor's proposed labeling for this product is attached to this review as Appendix A.

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BACKGROUND:
Diclofenac sodium (Voltaren) currently is approved for the acute and chronic treatment of signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Recommended dosing is as shown in the table below. In all cases the dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects.

Diclofenac® * Indications

Indication	Dosing
Osteoarthritis	100 to 150mg daily in divided doses (50mg b.i.d. or t.i.d. or 75mg b.i.d.) or 100mg q.d. of the extended release diclofenac formulation (Voltaren-XR)
Rheumatoid Arthritis	150 to 200mg daily in divided doses (50mg t.i.d. or q.i.d. or 75mg b.i.d.); a dose of 100mg q.d. is recommended for Voltaren XR and the dose rarely may be increased to 100mg b.i.d. if benefits outweigh risks. Dosages above 225mg/day are not recommended.
Ankylosing Spondylitis	100 to 125mg daily given as 25mg q.i.d. with an extra 25mg dose at bedtime if needed

* Diclofenac currently is available as three products. These are: VOLTAREN® (diclofenac sodium) Delayed Release (enteric-coated) Tablets, available in 25, 50, and 75mg sizes; CATAFLAM® (diclofenac potassium) Tablets, available in 50mg size; VOLTAREN-XR® (diclofenac sodium) Extended-Release Tablets available in 100mg size.

Throughout this review, the diclofenac referred to is enteric-coated sodium salt.

reviewer's original table, based on information in the current labeling for diclofenac products. (See Appendix B).

Misoprostol (Cytotec®) currently is approved for prevention of NSAID (including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g. the elderly and patients with concomitant debilitating disease, as well as patients with a high risk of developing gastric ulceration, such as patients with a history of ulcer. The recommended misoprostol dose is 200mcg four times daily with food; the last dose of the day should be taken at bedtime. Though not yet approved for prevention of duodenal ulcers in patients taking NSAIDs, misoprostol has been recommended by the FDA as approvable for this indication at a dose of 200mcg q.i.d. If the 200mcg q.i.d. dose cannot be tolerated, 200mcg t.i.d. may be used for the prevention of NSAID-induced gastric ulcer (See Division's approvable letter to the sponsor dated June 6, 1996 and attached to this review as Appendix C). A copy of the currently approved misoprostol (Cytotec) labeling is attached as Appendix D.

MATERIALS REVIEWED:
This submission consists of 353 volumes. Contents of the volumes are as listed below:

- Vol. 1.1 — Index
- Vol. 1.2 — Summary (including proposed labeling, summaries of major submission sections, and benefit/risk discussion)
- Vols. 1.3 through 1.10 — Chemistry, Manufacturing and Controls
- Vol. 1.11 — Samples, Methods Validation and Labeling
- Vols. 1.12 through 1.26 — Nonclinical Pharmacology and Toxicology
- Vols. 1.27 through 1.46 — Human Pharmacokinetics and Bioavailability
- Vols. 1.47 through 1.129 — Clinical Data Section
- Vols. 1.130 through 1.176 — Statistical Section
- Vols. 1.177 through 1.217 — Case Report Tabulations
- Vols. 1.218 through 1.352 — Case Report Forms
- Vol. 1.353 — Patents, Patent Certification and Other Information

Also, information and data from the clinical trials have been submitted to the Division in an electronic format (CANDA).

The sponsor has submitted reports of 7 "pivotal" clinical studies to support the efficacy and safety of Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg) and/or Arthrotec 75 (diclofenac 50mg/misoprostol 200mcg) for treatment of signs and symptoms of arthritis with concurrent prevention of gastric and duodenal ulcers. Also, there are 5 additional "supportive" efficacy and safety studies. The Arthrotec formulations used in these trials were not the same as the formulations the sponsor intends to market.

The Arthrotec formulations the sponsor intends to market contain diclofenac sodium in an enteric-coated core and misoprostol dispersed in a the enteric-coated core. The following table lists the 7 "pivotal" and 5 "supportive" studies:

Summary of Efficacy Studies

Disease Population	Study	Study Medication Doses[a] (treatment duration)	Comments
Osteoarthritis	IN2-89-02-296	A50 b.i.d./t.i.d. vs diclofenac (4 weeks)	-----
Osteoarthritis	IN2-89-02-298	A50 b.i.d./t.i.d. vs diclofenac (4 weeks)	
Osteoarthritis	IN2-90-02-321	A50 b.i.d. vs piroxicam or naproxen (4 weeks)	

Osteoarthritis	NN2-94-02-349	A50 t.i.d., A75 b.i.d., vs diclofenac 75mg b.i.d. vs placebo [6 weeks]	
Rheumatoid arthritis	IN2-89-02-289	A50 b.i.d./t.i.d. vs diclofenac [12 weeks]	
Rheumatoid arthritis	IN2-89-02-292	A50 b.i.d./t.i.d. vs diclofenac [12 weeks]	
Rheumatoid Arthritis	NN2-94-02-352	A50 t.i.d. and A75 b.i.d. vs diclofenac vs placebo [12 weeks]	
Osteoarthritis or Rheumatoid Arthritis	EB2-87-02-269	*diclofenac 50mg* + misoprostol 200mcg b.i.d./t.i.d. vs diclofenac b.i.d./t.i.d. [52 weeks]	
Ankylosing spondylitis	IN2-89-02-304	A50 b.i.d./t.i.d./q.i.d. vs *diclofenac* [8 weeks]	
Musculoskeletal disorders	IN2-90-02-305	A50 b.i.d./t.i.d. vs diclofenac [14 days]	
Musculoskeletal disorders	EN2-91-02-306	A50 t.i.d. vs diclofenac [7 days]	
Long-term safety study	IN2-89-02-297	A50 b.i.d./t.i.d. [24 months]	

* A50 = Arthrotec 50 = Arthrotec I (diclofenac 50mg/misoprostol 200mcg);
A75 = Arthrotec 75 = Arthrotec II (diclofenac 75mg/misoprostol 200mcg);
Where no diclofenac dose is indicated, the dose in mg is the same amount as in the combination treatment being studied.

* For these studies the manufacture dates and lot numbers were different (earlier) than those of used in the other clinical trials and in the bioequivalence studies.

reviewer's original table

Results of the 5 clinical trials in which endoscopy was done to examine ulcer rates in arthritis patients treated with diclofenac/misoprostol combination as compared to rates in arthritis patients treated with NSAID alone are presented and discussed below. In addition, Study 352, in which endoscopy was not done but which was one of the two studies using the diclofenac/misoprostol formulations most similar to those the sponsor intends to market, is discussed. (The sponsor's efficacy results for treatment of arthritis signs and symptoms are stated briefly but are not discussed here. Antiarthritic efficacy is being

addressed by the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products).

BIOEQUIVALENCE STUDIES:
A number of different formulations of Arthrotec were studied during the drug development process. None of the clinical trials used the exact products the sponsor intends to market.

Because the clinical trial formulations were not the formulations the sponsor intends to market, the sponsor has attempted to link the trial formulations to the formulations proposed for marketing [Arthrotec 50 and Arthrotec 75 through bioequivalence studies. These studies have been reviewed by the Division of Pharmaceutical Evaluation (Dr. H-RChoi). Findings for diclofenac and misoprostol acid AUC and C_{max} are summarized in the table below. [Note: For misoprostol, misoprostol acid, the active metabolite of misoprostol, was measured]. For bioequivalence to be established, the ratio of the test product values to the standard product values the 90% confidence interval should be within the range of

Summary of Some Important Bioequivalence Study Results

Comparison	Study	Diclofenac		Misoprostol Acid	
		ratio AUC (90% CI)	ratio Cmax (90% CI)	ratio AUC (90% CI)	ratio Cmax (90% CI)
Arthrotec 50:					
	343	96.9% (91.2%, 102.9%)	87.6 (80.1%, 95.8%)	104.5% (96.8%, 112.9%)	103.7% (93.1%, 115.4%)
	332	112.7% (106.0%,119.9%)	88.7% (79.3%, 99.2%)	95.8% (84.1%,109.1%)	97.2% (85.9%, 110.0%)
	354	102.0% (92.1%, 112.9%)	100.3% (81.3%, 123.8%)	106.0% (94.0%, 119.6%)	87.8% (75.2%, 102.6%)
	354	97.7% (88.2%, 108.4%)	97.5% (79.0%, 120.3%)	97.4% (86.7%, 109.4%)	99.8% (85.4%, 116.6%)
	345	98.9% (91.2%, 107.4%)	89.5% (77.5%, 103.3%)	87.8% (83.0%, 93.0%)	83.7% (77.9%, 89.8%)
Arthrotec 75:					
	353	100.7% (91.3%, 111.1%)	100.3% (88.4%, 113.7)	102.1% (96.0%, 108.6%)	103.2% (91.4%,116.6%)
	346	108.6% (93.6%, 125.9%)	75.9% (60.5%, 95.2%)	112.8% (101.5%, 125.4%)	113.4% (95.5%, 134.6%)

CI = confidence interval

reviewer's original table based on information in Clinical Pharmacology and Biopharmaceutics Review dated 10/31/96

Arthrotec 50: For Arthrotec 50 no direct bioequivalence comparison was made between the formulation used in the pivotal trials , II, Study 349 and Study 352] and

marketed Cytotec + Voltaren. Rather the sponsor has linked these formulations through two bioequivalence studies. was compared to (Study 343) and FDA Biopharmacetutics found these to be bioequivalent with respect to both diclofenac AUC and Cmax and misoprostol AUC and Cmax. was also compared to marketed Cytotec + Voltaren (Study 332). In that study, the confidence intervals for ratios of the misoprostol and diclofenac AUCs and for misoprostol Cmax were within an acceptable range; however, the lower limit of the confidence interval for the ratio of Cmax of diclofenac fell slightly outside the range. FDA Biopharmaceutics concluded, "Arthrotec 50 is bioequivalent to Voltaren alone for diclofenac AUC and Cmax; Arthrotec 50 mg is also bioequivalent to Cytotec alone for misoprostol acid AUC and Cmax." (Dr. H.-R. Choi, Clinical Pharmacology and Biopharmaceutics Review, dated 10/31/96, p.19). Therefore, it seems reasonable to me to conclude that, gastrointestinal protective efficacy information from the misoprostol efficacy information for Study 349 should be applicable to Cytotec as well, and the same should be true for the antiarthritic efficacy in Studies 349 and 352 and Voltaren.

For Arthrotec 50 there was no direct or indirect bioequivalence comparison of the product proposed for marketing and to either already marketed Cytotec + Voltaren or to the pivotal clinical trial formulation . was compared to the Arthrotec 50 formulation (Study 354). The ratio Cmax for Proposed Product B fell below the lower range allowed. FDA Biopharmaceutics review concluded that Arthrotec 50 and proposed Product B were bioequivalent with regard to diclofenac but not with regard to misoprostol acid rate of absorption. [Another study (Study 345) of a formulation identical to except for diclofenac supplier also failed to demonstrate bioequivalence of the product to the formulation]. The sponsor did not compare the formulation to any other Arthrotec formulations. The sponsor states: "The indirect bioavailability link was established via the marketed Arthrotec[R] tablets which were identical to clinical supply II with exception of misoprostol dispersion (duplex vs. simplex) and the site of manufacture (Figure 8). The duplex vs. simplex dispersion process, however, had no impact on the bioavailability of misoprostol. This was established not only with Cytotec[R] tablets (study NB2-87-02-280) but also in the development of Arthrotec[R] tablets from switching (NDA Vol. 1.2, p. 2-165). [Sponsor's Figure 8 is attached as Appendix E]. It should be noted that Clinical Supplies I and II differ from each other in several regards (i.e., manufacturing site, diclofenac source, size, in addition to dispersion process. In this reviewer's judgement the information provided is not sufficient to justify an assumption of bioequivalence between Arthrotec and (and thereby to Cytotec + Voltaren). Therefore, approval of the proposed Arthrotec 50 formulation cannot be based on efficacy data from clinical trials of Cytotec.

Arthrotec 75: For Arthrotec 75, the drug used in the clinical trials was compared with regard to both diclofenac and misoprostol to the product the sponsor intends to market and the two formulations were found to be bioequivalent. In another study (Study 346) was <u>not</u> bioequivalent to already marketed

Cytotec + Voltaren. There was no direct bioequivalence study comparison of Product conncurrently administered marketed Cytotec + Voltaren. However, based on bioequivalence Studies 353 and 346, Product would supply on average about 13% more diclofenac AUC but have a Cmax for diclofenac about 93% that of Voltaren and it would supply on average about 8% more misoprostol AUC and have a Cmax equal to 108% that of Cytotec [personal communication, Dr. H-RChoi, FDA Biopharmaceutics]. Therefore, based on these bioavailability studies, while efficacy results seen with the product used in the clinical trials should be extrapolatable to the Arthrotec 75 product intended for marketing (Product efficacy results from studies of Cytotec alone and Voltaren alone may not be directly applied as pivotal studies to support the approval of Arthrotec 75 (US Product C).

CHEMICAL COMPOSITION OF ARTHROTEC FORMULATIONS PROPOSED FOR MARKETING:

Chemical composition of the Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg) and Arthrotec 75 (diclofenac 75mg/misoprostol 200mcg) intended for marketing are given in the table below:

Composition of Arthrotec Formulations Intended for Marketing

	Amount* Per Tablet (mg)	
	Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg)	Arthrotec 75 (diclofenac 75mg/misoprostol 200mcg)
Diclofenac Sodium		
Lactose		
Starch (Corm)		
Polyvidone (Povidone) K-30		
Magnesium Stearate		
Methacrylic Acid Copolymer		
Sodium Hydroxide		
Talc		
Triethyl Citrate		
Misoprostol		
Microcrystalline Cellulose		
Crospovidone		
Hydrogenated Castor Oil		
Total Tablet		

REVIEW OF CLINICAL STUDIES:

I. **Protocol: NN2-94-02-349:** A Comparative Study of the Efficacy and Upper Gastrointestinal Safety of Diclofenac 50mg/Misoprostol 200mcg TID, and