

fingers, legs and tail, (males and females of the mid and high dose combination and high dose diclofenac groups). Finally, the Sponsor stated that instances of convulsions and prostration were observed in a few animals during drug administration. However, individual animal data regarding these latter observations were not provided. The onset and duration of clinical signs were not reported, but were stated not to be present during the reversal phase.

2. **Mortality:** Treatment-related mortality was seen in 1 high dose combination (HC) male (No. 87-6879) which died in week 14. In addition, 1 high dose diclofenac (HD) male (No. 87-6904) and 2 HD females (Nos. 87-6907 and 87-6908) were killed in extremis at weeks 4 and 14, and 2, respectively. Finally, one high dose combination female (No. 87-6885) died in week 18, with death attributed to an intubation error.

4. **Body Weight/Food Consumption:** Mean body weight loss of 6%, (compared to day -4 body weights) were observed in high dose diclofenac males and in the high dose diclofenac. In comparison, control males and males in the high dose combination treatment groups exhibited mean body weight gains of 16 and 19%, respectively. Body weight loss was also seen in 1 female per each high dose group, while, complete suppression of body weight gain was also seen in 1 female each in the mid and high dose combination groups. In comparison, control females exhibited mean body weight gains of 9.68% compared to day -4 body weights. One high dose diclofenac male and 2 high dose diclofenac females which died or were killed in extremis prior to completion of the treatment also showed body weight loss of or complete suppression of body weight gain. Data on the effects of treatment on food and water consumption were not provided.

5. **Hematology:** Treatment-related hematological alterations which were evident at the end of the treatment period (week 25) included: decreased red blood cells (12.2% and 13.2%); hemoglobin (24 and 8%) and hematocrit (14.8 and 4.9%) in males in the high dose diclofenac and combination groups, respectively. High dose diclofenac males also exhibited reduced mean corpuscular volumes (13.7%) and reduced mean corpuscular hemoglobin concentrations (13.8%). Other treatment-related findings included: increased reticulocytes (0.8% and 1.1%) in high dose diclofenac males and females compared to values of 0.5% and 0.2% in control males and females, respectively. Monkeys in both high dose treatment groups also had increased neutrophils; (% and absolute; 41-80%) and decreased lymphocytes (% and absolute; . Finally, increased platelet counts were seen high dose diclofenac males (126.6% from control values of  $387 \times 10^9/L$ ) and females (31.8%) and in high dose combination males (26%). Partial reversal of the aforementioned changes were observed in animals which underwent recovery, with the exception of reticulocytes which remained elevated in the high dose diclofenac group (males and females 100 and 233%, respectively).

6. Blood Chemistry: Treatment-related effects on blood chemistry included: decreased albumen ( ) in the mid and high dose combination groups and ( ) in the high dose diclofenac groups, increased globulin ( ) in the high dose diclofenac group, and decreased albumin to globulin ratios ( ) in the high dose diclofenac group and ( ) in the mid and high dose combination groups. Additional treatment-related effects included: decreased calcium ( ) both sexes in the high dose diclofenac group and males in the high dose combination group); increased chloride (1.8 to 4.5%) in low and high dose diclofenac groups and in the mid and high dose combination groups; increased triglycerides (30 and 100% in low and high dose diclofenac males and 50% and 79% in high dose diclofenac and combination females, respectively); decreased aspartate aminotransferase ( , both sexes in both high dose groups); decreased alanine aminotransferase ( ) all treatment groups except females in both low dose groups); decreased alkaline phosphatase ( , in individual males and females in the mid and high dose combination groups and in the high dose diclofenac groups), except for one high dose combination male which had increased alkaline phosphatase activity (236% compared to a mean control values of 1460 IU/l); increased urea ( , males in both high dose groups and 27-54% in females in all treated groups); and increased creatinine levels (21%, in high dose diclofenac males and (13%, 28% and 38% in females in the low and high dose diclofenac groups and in the high dose combination groups, respectively. The high dose diclofenac female, (No. 87-6908), which was killed in extremis during week 2 also showed dramatic changes in blood biochemistry (i.e. large increases in plasma urea, creatinine, triglycerides, potassium, aspartate aminotransferase, and globulin and decreased albumin, total protein, calcium and chloride) indicative of acute renal failure. With the exception of chloride levels, which remained elevated in low and high dose diclofenac animals (2.7%), all other changes in blood chemistry were not observed following the recovery period.

7. Urinalysis: Urinalysis was not indicated.

8. Physical/Electrocardiographic/Ophthalmologic Examinations:

No treatment-related changes in rectal temperature were observed. Other observations made during physical examinations (i.e. loose stools, salivation, wounds) are reported under Observed Effects (above). Various electrocardiographic differences including: reductions in P wave amplitude (low dose combination group versus low dose diclofenac group); decreased heart rate and/or increased QT intervals (mid dose combination group and low dose diclofenac group versus controls); slight decrease in PQ and QT (mid dose combination group compared to controls) and persistent sinus arrhythmia with a low heart rate (96 bpm) at week 24 (1 low dose diclofenac male) were observed. However, ECG changes were not dose-related and did not occur in high dose groups. Therefore their relationship to treatment is unknown. Several ophthalmoscopic observations were noted, however, these appeared incidental in nature, since they occurred sporadically and were not dose related.

**9. Organ Weights:** Treatment-related changes in absolute and/or relative weights for organs are summarized in Table 4, (succeeding page). Briefly, treatment-related changes in organ weights occurred mainly in males of both high dose groups and included: 1) increased relative weights (organ to body weight ratios) for liver and kidney; 2) decreased absolute and relative weights for testes, epididymis, and prostate (HD only); and 3) decreased absolute and relative weights for thymus in HD). In comparison, high dose females (HD and HC) only showed decreased absolute and relative weights for uterus. At the end of the reversal period kidney weights (absolute and relative) remained mildly elevated ) but only in the HC group. Treated males which underwent the recovery period showed a dramatic rebound in absolute and relative weights for reproductive organs (testes, epididymis and prostate).

**TABLE 4. Treatment-related changes in absolute and/or relative (organ/final body weight [ORG/FBW]; and organ/brain weight [ORG/BRN]) organ weights for male and female monkeys (expressed as a percent change from respective control values).**

SEX	Organ	Dose	Absolute	Relative Weights	
			Δ‡ in Wt	Δ‡ ORG/FBW	Δ‡ ORG/BRN
M	Liver	LD	----	↑ 11*	----
		HD	----	↑ 19*	----
		HC	----	↑ 18*	----
M	Kidney	HD	----	↑ 19*	----
		HC	----	↑ 19*	----
M	Testes	LD	↓ 28	↓ 35	↓ 29
		HD	↓ 67*	↓ 62	↓ 64
		HC	↓ 70*	↓ 69	↓ 71
M	Epididymis	LD	↓ 16	----	----
		HD	↓ 47*	↓ 33	↓ 33
		HC	↓ 37*	↓ 33	↓ 33
M	Prostate	HD	↓ 27	----	↓ 50
M	Pituitary	MC	↑ 28*	↑ 21	↑ 33
		HC	↑ 35*	↑ 41	↑ 33
M	Thymus	HD	↓ 66	↓ 57	↓ 57
F	Uterus	HD	↓ 49	↓ 42	↓ 50
		HC	↓ 29	↓ 20	↓ 25

\* = Statistically significant change from control values.

---- = Comparable to control values

↑ or ↓ = increased or decreased relative to mean control weights

LD = Low Dose Diclofenac (6 mg/kg)

HD = High Dose Diclofenac (50 mg/kg)

LC = Low Dose Combination Misoprostol:Diclofenac (24 ug:6 mg/kg)

MC = Mid Dose Combination Misoprostol:Diclofenac (68 ug:17 mg/kg)

HC = High Dose Combination Misoprostol:Diclofenac (200 ug:50 mg/kg)

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Increased absolute and relative organ weights for recovery males were as follows: 1) for testes (increases 140-220% in Low Dose Diclofenac group [LD], in HD, in low dose combination [LC] groups, in mid dose combination [MC] groups, and in HC); epididymis in HD, 33-60% in LC, in MC and in HC); and prostate (50-100% in LD, in HD, in LC, in MC and in HC) Finally, recovery males exhibited increased absolute and relative weights for adrenal glands ( in HD) and dose-dependent decreases in absolute and relative weights for thymus ( in HD, in MC and in HC). HD recovery females also showed increased absolute and relative weights for ovaries ( ) and thymus ( ) and decreased absolute and relative weights for uterus ( . In comparison, HC recovery females only showed increased absolute and relative pituitary weights ( %).

**10. Gross Pathology:** Gross pathological findings in animals which died or were sacrificed in extremis (1 male and 2 females in the high dose diclofenac groups and 1 male in the high dose combination group) included one or more of the following: ulcers/erosions of the skin, hemorrhage in the stomach, ulcer(s) in the duodenum, discoloration of the jejunum, colon, heart, kidney and/or lung, enlarged lymph nodes, and fibrous adhesions in the lung, liver, heart (pericardial adhesion) and brain (meningeal adherence).

Gross findings in animals sacrificed at the end of the treatment included: 1) hyperemia and or hemorrhage of the cecum and duodenum (2 of 3 males and 2 of 3 females in the high dose diclofenac [HD] groups, and 1 of 4 females in the mid dose combination [MC] group), 2) hyperemia of the jejunum was also seen in 1 of the 2 aforementioned HD females; 3) enlarged lymph nodes (2 of 3 HD males); 4) fibrous adhesions/plaques around the stomach and/or liver were also seen in 1 of 3 HD males and 1 of 4 LD males. In addition, treated males exhibited an overall increased incidence of nodules (brown or hyperemic) in the cecum, colon and/or jejunum (2 of 6 MC males, 3 of 6 HC males, 3 of 6 LD males and in 1 of 6 HD males versus 0 of 6 males each in the control and low dose combination groups). In contrast, the incidence of these types of nodules in treated females was comparable to that seen in control females. Gross pathological changes observed in recovery animals included: hyperemia of the cecum (1 of monkey/sex in the HD group and 1 of 2 males in the HC group. Other gross pathological findings, such as the presence of parasites (*Oesophagostomum* spp.), and a limited incidence of enlarged ovaries, spleen, thymus and thyroid occurred either at comparable incidence in control animals or sporadically.

11. **Histopathology:** Treatment-related histological changes in animals which died or were sacrificed in extremis (1 male and 2 females in the high dose diclofenac groups and 1 male in the high dose combination group) included one or more of the following: peritonitis of the stomach, duodenum or liver; congestion of the duodenum, jejunum and colon; mucosal ulcerations in the cecum and or duodenum and ulcerations of the skin. One or both of the aforementioned high dose diclofenac females also exhibited cortical tubular dilation and glomerulonephritis of the kidney, acute sinusoidal congestion of the spleen, reactive hyperplasia/nonspecific lymphadenitis in the mesenteric lymph node, fibrous adhesions of the lungs and acute myocarditis and pericarditis. Whereas the aforementioned HD male which died showed portal subacute inflammation in the liver, sinusal edema in the mesenteric lymph node, acute myocarditis, acute testicular inflammation and degeneration, and epididymitis.

Treatment-related histological findings observed in monkeys sacrificed at the end of the treatment period included: mucosal ulceration/peritonitis of the stomach (1 of 4 HD males), duodenum (1 of 4 HD males), and cecum (3 of 4 MC females, 2 of 3 males and 3 of 3 females each, in the HC group and HD groups); mucosal hemorrhage in the cecum (1 of 3 HD males); cortical tubular dilation of the kidney (1 of 4 MC females, 2 of 3 HC females and 1 monkey/sex in the HD group); glomerulonephritis 1 of 3 females each at the HC and HD groups); peritonitis in the liver (1 of 3 HD males); portal subacute inflammation of the liver (1 of 4 LD males and 1 of 3 HD females); lymphoid hyperplasia of the spleen (1 of 4 LC males, 1 of 3 males and 2 of 3 females in the HC group, 1 of 4 LD females and 2 of 3 monkeys/sex in the HD group); increased incidence of reactive hyperplasia/nonspecific lymphadenitis in the mesenteric lymph node (2 of 3 HC males, 3 of 3 HD males and 2 of 2 HD females versus none of 4 males and only 1 of 4 female control animals) and sinusal edema in the mesenteric lymph node (1 of 3 HC males).

Histological observations in recovery monkeys included: mucosal hemorrhage of the cecum (2 of 2 HC males and 1 of 2 males each in the LD and HD groups; and lymphoid hyperplasia of spleen (1 monkey/sex in the LD group); myeloid hyperplasia of the spleen (both HC recovery males); reactive hyperplasia/nonspecific lymphadenitis and sinusal edema of the mesenteric lymph nodes (1 of 3 MC males and 1 of 2 HC females, respectively). Intralobular hemorrhage of the thymus (both HC recovery females) and myositis of the skeletal muscle (one of 2 recovery females each in the HC and HD groups) were also seen in recovery animals. However, neither of these findings were observed in animals at the end of the treatment period.

**12. Plasma Levels of the Drug:** Data on the absorption of orally administered diclofenac, alone or in combination with misoprostol on days 1, 85 (week 13), and 176 (week 26) in monkeys is presented in Table 5, (succeeding page). Briefly, diclofenac and the combination of diclofenac and misoprostol were rapidly absorbed following oral dosing with maximal plasma levels of diclofenac attained between 0.25 and 1.21 hr in all dose groups. The addition of misoprostol did not affect absorption or pharmacokinetics of diclofenac, with the possible exception of females in the high dose combination group on day 176, where Cmax and AUC values were approximately double those seen in the high dose diclofenac group. Increases in plasma concentrations and AUC values on days 1, 85 (week 13) and 176 (week 26) appeared linear but disproportional to dose (greater than expected) in both groups, with no sex-related differences observed. Finally, there was no evidence of accumulation with repeated dosing since, plasma concentrations and AUC values tended to be some what lower (both sexes) on day 176 compared to day 1 of dosing.

**Table 5. Mean Cmax and AUC values for Diclofenac in Plasma in Cynomolgus Monkeys Following Oral Administration of Diclofenac Alone or in combination with misoprostol on Days 1, 85, and 176.**

Group #	Sex	Cmax (ug/ml)			AUC (ug·hr/ml)		
		Day 1	Day 85	Day 176	Day 1	Day 85	Day 176
Control	M	0.0	0.0	0.0	0.0	0.00	0.0
LD	M	5.0	3.89	4.5	5.9	5.97	5.1
HD	M	88.1	50.19	44.5	225.0	125.48	132.3
LC	M	5.0	5.22	7.0	8.0	6.64	8.6
MC	M	28.7	14.30	12.1	40.8	28.53	22.7
HC	M	111.4	70.38	61.7	219.9	169.11	150.7
Control	F	0.0	0.00	0.0	0.0	0.00	0.0
LD	F	5.0	6.24	3.6	6.6	6.24	4.5
HD	F	100.5	35.40	25.3	200.2	76.35	53.2
LC	F	7.4	2.46	4.8	9.9	2.79	5.6
MC	F	25.4	12.88	15.7	36.5	20.71	21.8
HC	F	93.9	37.42	48.6	202.2	101.16	104.4

Control = Vehicle controls

LD = Low dose Diclofenac [6 mg/kg]

HD = High dose Diclofenac [50 mg/kg]

LC = Low dose Diclofenac/misoprostol [6 mg/kg: 24 ug/kg]

MC = Mid dose Diclofenac/misoprostol [17 mg/kg:68 ug/kg]

HC = High dose diclofenac/misoprostol [50 mg/kg:200 ug/kg]

The instability of SC-30695 (the main metabolite of misoprostol) and other analytical problems prevented obtaining full results for absorption of misoprostol. However, SC-30695 metabolite data from day 176 suggested that misoprostol was well absorbed with average plasma concentrations of 439 and 684 pg/ml, 1299 and 1183 pg/ml, and 2400 and 2120 pg/ml in male and female monkeys in the low, mid, and high dose combination groups, respectively.

In conclusion, misoprostol had no adverse toxicological interaction on the toxicity profile of diclofenac following 6-month oral administration in monkeys. Diclofenac alone or in combination with misoprostol produced treatment-related clinical signs including: reduced motor activity, prostration, convulsions, mild losses in body weights and death in both high dose groups. Alterations in hematology (males in both high dose groups and females in the high dose diclofenac group) and blood chemistry (both diclofenac groups and mid and high dose combination groups) were also observed. Urinalysis was not indicated. Target organs of toxicity included: 1) organs of the GI tract (i.e. stomach, duodenum, jejunum, cecum and colon), 2) kidney; and 3) the liver. Ulcerations of the skin, along with increased numbers neutrophils and decreased lymphocytes in high dose animals also suggested possible treatment-related effects on immune function. Toxic effects occurred in animals of the mid and high dose combination groups and the low and high dose diclofenac groups (no mid dose diclofenac group included) and were more prevalent and severe in males versus females and in the diclofenac versus combination groups. Pharmacokinetic analysis showed that in general, misoprostol did not affect the absorption or pharmacokinetics of diclofenac in the monkey. The low dose combination dosage 24  $\mu$ g/kg misoprostol plus 6 mg/kg diclofenac could be considered the no effect dose in the monkey.

**APPEARS THIS WAY  
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**MUTAGENICITY:****1. Ames Assay of Diclofenac Sodium/Misoprostol in Salmonella typhimurium (Study No. PSA-89S-3556)**

This study

the review follows:

A copy of

**Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) (Study No. S.A. 3556)****Testing Laboratories:**

**Study Started:** July 18, 1989

**Study Completed:** September 28, 1989

**GLP Requirements:** A Statement of compliance with the GLP regulations and quality assurance unit was included.

**Drug Batch No.:** Diclofenac, Lot No. 8935025  
Misoprostol, Lot No. 3D07510

**Methods:** The mutagenic activity of Misoprostol/diclofenac (1:250 ratio) at concentrations of 0.04/10, 0.2/50, 0.4/100, 2/500, 4/1000 and 20/5000 ug/plate, was tested in two independent studies using the AMES test (standard method); tester strains Salmonella typhimurium TA97, TA98, TA100, TA1535 and TA1538 in both the presence and absence of an S-9 mix (metabolic activation system). The basis of dose selection was not provided, however, a maximum concentration of 5000 ug/plate of test agent is standard for the assay system. Positive controls in tests without S-9 metabolic activation were: sodium azide (1 ug/plate) for test strains TA1535 and TA100, 2-nitrofluorene (2.5 ug/plate) for strains TA1538 and TA98, and IRC-191 acridine (0.5 ug/plate) for Strain TA97, whereas, 2-aminoanthracene (1 ug/plate) was used for all 5 strains in the presence of the S-9 metabolic activation system. Criteria for a positive mutagenic effect in the above assays was a dose-related increase in the mean number of revertants/plate of at least 2 times greater than the vehicle control at two or more successive doses.

**Results:** At the highest concentration of 20/5000 ug/plate, Misoprostol/diclofenac was cytotoxic, as evidenced by reduced or eliminated growth of background lawn. However, Misoprostol/ diclofenac, at concentrations ranging from 0.04/10 to 20/5000 ug/plate produced no treatment-related increases in the numbers of revertant colonies in any of the bacterial strains tested in the presence or absence of a S-9 metabolic activation system. In comparison, the positive controls produced the expected increases in histidine revertant colonies, supporting the validity of the study. Therefore, the combination of Misoprostol/diclofenac, tested negative for mutagenic activity (induction of revertant strains) in the Ames assay.

2. Mutagenic Potential of Diclofenac Sodium/Misoprostol in the CHO/HGPRT Assay (Study No. PSA-89S-3549)

This study

the review follows:

A copy of

CHO/HGPRT In Vitro Mammalian Cell Mutation Assay with Misoprostol/Diclofenac (Report No. S.A. 3549)

Testing Laboratories: G.D. Searle & Co., Skokie IL

Study Started: July 26, 1989

Study Completed: September 28, 1989

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Drug Batch No.: Diclofenac, Lot No. 8935025  
Misoprostol, Lot No. 3D07510

Methods: The ability of misoprostol/diclofenac to induce a mutation at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus was tested in cultured Chinese hamster ovary (CHO) cells. Briefly, CHO cells were exposed to misoprostol/diclofenac at a ratio of 1:250, and concentrations of 0.05/12.5, 0.40/100, 0.80/200, and 1/250 ug/ml misoprostol/diclofenac for approximately 20-24 hours in the absence of the S-9 metabolic activation system and approximately 4 hours in the presence of the S-9 metabolic activation system. Dose selection was based on a Range finding cytotoxicity tests, where cytotoxicity was observed beginning at concentrations of 0.06/15.6 ug/ml, with complete cytotoxicity observed at 1.00/250 ug/ml. Exposed cells were then subcultured at  $1 \times 10^6$  cells/100 mm dish (1 dishes/treatment culture) for the mutant expression cultures. Parallel Day 1 cytotoxicity tests were also conducted on subcultured cells (200 cells/dish; 4 dishes/treatment culture) which were fixed, stained, and scored after 7 days of incubation. Mutant expression cultures were incubated for 1 day in normal medium and for 6 days in a low serum medium. Cells were then changed to a complete medium and after 1 additional day subcultured into the mutant selection medium (Complete F12 medium plus 10 uM 6-thioguanine) at  $0.2 \times 10^6$  cells/100 mm dish and in the complete F12 medium at 200 cells/60 mm plate for the day 9 cytotoxicity test. Subcultured cells were allowed to grow for an additional 7 days and then fixed and stained. Colonies of 50 cells or more in the mutation and parallel cytotoxicity dishes were then scored for calculation of the mutation frequency and % cell survival, respectively. IRC-91 acridine (IRC; 1 ug/ml) and 3-methylcholanthrene (MCA; 5 ug/ml) were used as positive

controls in the absence and presence of the S-9 metabolic activation system, respectively. A test was considered positive if mutation frequencies were  $\geq 15$  per  $1 \times 10^6$  cloned cells for at least 2 successive test article concentrations and significantly higher than solvent controls.

**Results:** Results from the mutation experiment showed that Misoprostol/diclofenac produced a dose-dependent decrease in relative survival compared to vehicle control values from an average of 107% at 0.0.05/12.5 ug/ml to 26% at 0.40/100 ug/ml in the absence of metabolic activation and from 105% at 0.20/50 ug/ml to 22% at 1.00/250 ug/ml in the presence of the metabolic activation system. Misoprostol/diclofenac produced no evidence of increased mutagenesis in terms of an increased frequency of mutant cloned cells at any dose tested with or without activation (i.e. none of the mutant frequencies were greater than 15 per  $1 \times 10^6$  cloned cells and significantly different from controls). Both positive controls showed the expected increases in mutant frequencies (IRC = 186 mutants/ $10^6$  cloned cells and MCA = 162 mutants / $10^6$  cloned cells). Therefore, Misoprostol/diclofenac tested negative for mutagenicity in the CHO/HGPRT assay system.

3. Clasogenic Potential of Diclofenac Sodium/Misoprostol in the Rat Lymphocyte Chromosomal Aberration Assay (Study No. PSA-89S-3560)

This study

the review follows:

A copy of

Chromosomal Aberrations in Rat Peripheral Blood Lymphocytes  
(Study No. S.A. 3560)

Testing Laboratories: G.D. Searle & Co., Skokie IL

Study Started: August 15, 1989

Study Completed: September 28, 1989

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Drug Batch No.: Diclofenac, Lot No. 8935025  
Misoprostol, Lot No. 3D07510

**Methods:** A solution of misoprostol and diclofenac, at a ratio of 1:250, misoprostol/diclofenac, and was tested for clastogenic activity in cultured rat peripheral blood lymphocytes. Briefly, cultured rat lymphocytes were arrested at metaphase and examined for chromosomal aberrations including, chromosome and chromatid gaps, deletion/breaks, and exchanges, following exposure to the combination of misoprostol/diclofenac at concentrations of 12.5, 25, 37.5, 50 and 62.5 ug/ml (expressed as the concentration of diclofenac), for 17 hours in the absence of an Aroclor-induced S-9 activation system and for 2 hours in the presence of an Aroclor-induced S-9 activation system. The high dose level, 62.5 ug/ml was selected based on cytotoxicity in a range finding study, where the lowest concentration of misoprostol/diclofenac tested, 0.40/10 ug/ml decreased relative survival of the cells by 25 and 56% in the presence and absence of a metabolic activation system, respectively. Negative, vehicle (dimethylsulfoxide) and positive controls, triethylenemelamine (0.20 ug/ml), in the absence of the S-9 fraction and cyclophosphamide (7.5 ug/ml), in the presence of the S-9 fraction, were also included for validation of the studies. A separate study was conducted to determine the effects of misoprostol 0.001 /0.25 to 0.2/50 ug/ml (misoprostol/ diclofenac) with or without metabolic activation on cell cycle kinetics (mitotic index). A response was considered positive if the percent aberrant cells for at least two successive test article concentrations was significant or one dose level was significant with an indication of a dose response relationship compared to negative control values.

**Results:** Results from the cell cycle kinetics study showed that the presence and absence of the S-9 fraction, the high dose (0.2/50) misoprostol/diclofenac reduced the mitotic index by 38 and 64%, respectively, whereas lower doses tested (0.075/18.75 and 0.1/25 ug/ml) had minimal to no effects on cell cycle kinetics with or without the metabolic activation system. Mitotic indices in the clastogenicity study ranged from 1 to 11% in the misoprostol/diclofenac treated groups, compared to 17% in the negative vehicle controls indicative of severe to moderate cytotoxicity at the doses tested. However, each culture had at least 50 metaphase cells which were evaluated for clastogenicity. Evaluation of the three highest doses tested 0.15/37.5, 0.21/50 and 0.25/62.5 showed that in either the presence or absence of the metabolic activation system, none of the concentrations evaluated produced treatment-related increases in numbers of aberrant cells, relative to the DMSO control values. In contrast, the positive controls, triethylenemelamine and cyclophosphamide produced average incidence of 68% and 59% aberrant cells in the in the absence and presence of the S-9 fraction metabolic activation system, respectively. Therefore, misoprostol/diclofenac tested negative for clastogenic activity in the rat peripheral blood lymphocyte chromosome aberration assay.

4. Potential of Diclofenac Sodium/Misoprostol to Induce Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells (Study No. PSA-89S-3558)

This study

A copy of

the review follows:

Misoprostol/Diclofenac: Micronucleus Test in Mice Following Oral Administration (Study No. S.A. 3558)

Testing Laboratories: G.D. Searle & Co., Skokie IL

Study Started: July 27, 1989

Study Completed: September 28, 1989

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: Male and female Cr:CD<sub>1</sub> Mice, approximately 6 weeks of age; weighing between 23 and 35 g.

Drug Batch No.: Diclofenac, Lot No. 8935025  
Misoprostol, Lot No. 3D07510

Methods: Misoprostol and Diclofenac were dissolved in a 25% polyethylene glycol 400 solution at a ratio of 1:250 and administered to groups of 12 mice (6/sex) twice by oral gavage, 24 hours apart, at doses of 0.12/30, 0.24/60 and 0.48/120 mg/kg/day of misoprostol/diclofenac. Dose selection was based on lethality of (misoprostol/diclofenac) at doses  $\geq$  0.8/200 mg/kg (misoprostol/diclofenac) in a previous dose range finding study in mice (Report No. PSA-89S-3557). The high dose level 0.48/120 mg/kg/day (misoprostol/ diclofenac) was selected as a dose level expected to produce some clinical signs of toxicity without excessive mortality. The lower doses were selected at half fold intervals from the high dose. Both negative (vehicle) and positive (cyclophosphamide, 20 mg/kg/day) controls were concurrently tested. Mice at each dose level were killed at approximately 24 hours after the second dose, followed by harvest and examination of the bone marrow for chromosomal damage in polychromatic erythrocytes (PCEs, approximately 1000/animal), as indicated by the presence of micronuclei. A test result was considered positive if a statistically significant increase in the frequency of micronucleated PCEs, relative to the concurrent vehicle controls. A test was considered negative if the criteria for a positive response were not met.

**Results:** The high dose of Misoprostol/Diclofenac (0.48/120 mg/kg/day) was lethal in 1 male and 2 female mice. Thus only 4 female mice were evaluated at the high dose. Since no indication of a sex related difference in micronuclei induction, values for male and female mice were pooled for statistical comparisons. Results from these tests showed no significant increases in the frequencies of micronuclei in any of the test-article treated groups compared to concurrent controls. In contrast administration of cyclophosphamide induced a significant increase in the frequency of micronucleated PCEs supporting the validity of the test. Evaluation of the relative proportions of polychromatic cells to total erythrocyte population also suggested that Misoprostol/Diclofenac had no cytotoxic or cytostatic effects at dose levels of 0.12/30, 0.24/60 and 0.48/120 mg/kg/day of misoprostol/diclofenac in mice. Therefore, under the current test conditions that the combination of Misoprostol/Diclofenac had no clastogenic, cytotoxic or cytostatic effects (measured in terms of PCE micronuclei and erythrocyte maturity) in mice at i.v. doses 0.12/30, 0.24/60 and 0.48/120 mg/kg/day (misoprostol/diclofenac).

#### REPRODUCTIVE TOXICOLOGY:

1. Segment II Oral Teratogenic Study of Diclofenac Sodium/Misoprostol in Rabbits (Study No. PSA-87S-3110)

This study

review follows:

A copy of the

Dose-Range Finding Studies of misoprostol/diclofenac in Rabbits

Testing laboratory: Sponsor at Skokie facility.

Date of the study: Nov. 4-Dec. 3, 1986 (1st study) and March 10-April 8, 1987 (2nd study).

In the first study, misoprostol/diclofenac were administered to six groups of 6 rabbits each from days 6 through 18 of gestation period at dosage levels of 40 mcg/kg/day misoprostol/ 10 mg/kg/day diclofenac, 120 mcg/kg/day misoprostol/30 mg/kg/day diclofenac, and 400 mcg/kg/day misoprostol/100 mg/kg/day diclofenac. Three other groups each received diclofenac alone at dosage levels of 10, 30, and 100 mg/kg/day. A control group received vehicle (0.5% methylcellulose and 0.1% polysorbate 80 in distilled water). There were drug-related clinical signs of low food intake, not eating and loose stools in all drug-treated groups. There were mortalities in all treatment groups except in the low combination group. There was an increase in numbers of resorptions for all drug-treated groups.

In the second dose-range finding study, dosage levels used were: vehicle control, 4 mcg/kg/day misoprostol/1 mg/kg/day diclofenac, 12mcg misoprostol/3 mg/kg/day diclofenac, 40 mcg/kg/day/10 mg/kg/day diclofenac, 1,3, or 10 mg/kg/day of diclofenac alone. There were no deaths, clinical signs and maternal body weight changes in any drug-treated groups. There were no adverse effects on numbers of corpora lutea, implantations, resorptions and live or dead fetuses in any drug-treated groups.

#### Segment II Teratologic Study of Misoprostol/Diclofenac in Rabbits

Testing laboratory: Sponsor's facility at Skokie.

Date of the study: May 5 to June 11, 1987.

GLP requirement: A statement of compliance with GLP regulations was included. However, quality assurance statement was not included.

Animals: New Zealand White rabbits weighing 3.1 to 3.9 kg were used.

Methods: Four groups of animals each consisting of 15 artificially inseminated pregnant rabbits were given vehicle, 4 mcg/kg/day misoprostol/1 mg/kg/day diclofenac, 12 mcg/kg/day misoprostol/3 mg/kg/day diclofenac, and 40 mcg/kg/day misoprostol/10 mg/kg/day diclofenac orally on days 6 through 18 of gestation period. The doses of misoprostol (batch no 01300) and diclofenac (lot # C0785) were prepared as fresh daily suspensions in a volume of 4 ml/kg. All fetuses were subjected to visceral and skeletal examinations.

#### Results:

Mortality: One animal in the high combination died due to drug-related effect. Additional four animals, two each from the control and low combination died due to intubation errors.

Clinical signs: Low food intake was seen in the high combination group.

Body weight: In the high combination groups, there was a significant retardation (43%) in maternal body weight gain.

Dams: In the high combination group, there was a significant increase (7 times) in number of resorptions. No adverse effects on fetal weight were seen at any dosage level. There were no abnormal external, visceral and skeletal findings in the study.

In conclusion, no teratogenic effects due to combined treatment were observed in rabbits at dosage levels up to 40 mcg/kg/day misoprostol and 10 mg/kg/day diclofenac equivalent to 2.5 times the recommended maximum human dose. Significant retardation in body weight and increase in resorption numbers were reported in the females of high combination group.

4 Page(s) Redacted

DRAFT Labeling

**Diclofenac Sodium**

Clinical signs that may indicate diclofenac sodium overdose include GI complaints, confusion, drowsiness or general hypotonia.

**Misoprostol**

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension or bradycardia.

**ARTHROTEC®**

Symptoms of ARTHROTEC® overdosage should be treated with supportive therapy. In case of acute overdosage, gastric lavage is recommended. Induced diuresis may be beneficial because diclofenac sodium and misoprostol metabolites are excreted in the urine. The effect of dialysis on the elimination of diclofenac sodium (99% protein bound) and misoprostol acid remains unproven. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

**SUMMARY AND EVALUATION:**

Diclofenac sodium is a NSAID derivative and possesses anti-inflammatory, analgesic and antipyretic activity. The more predominant adverse effects of diclofenac sodium include the production of peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is currently marketed in the U.S. and is indicated for the acute and chronic treatment of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Diclofenac sodium is available in a delayed-release formulation (Volataren®) and an immediate-release formulation (Cataflam®); Cataflam® is also indicated for the management of pain and primary dysmenorrhea.

Misoprostol is a prostaglandin E<sub>1</sub> derivative; it possesses antisecretory (inhibiting gastric acid secretion) and mucosal protective properties. Misoprostol is contraindicated in pregnant women because of its abortifacient property. Misoprostol (Cytotec®) is currently marketed in the U.S. and is indicated for the prevention of NSAID-induced gastric ulcers in patients at high risk of developing gastric ulceration.

Thus, it is apparent that there are some patients who receive concurrent diclofenac sodium and misoprostol medication. However, the sponsor suggests that the effectiveness of coadministration of diclofenac sodium and misoprostol is limited by (1) inconvenience to the patient of taking two sets of

medication, (2) possible mismatching of the diclofenac sodium dosing regimen and the misoprostol dosing regimen, and (3) incidence of adverse effects associated with the currently recommended 200 mcg qid dose of misoprostol (800 mcg/day).

Therefore, the sponsor is seeking approval for the marketing and use of ARTHROTEC<sup>®</sup> (fixed combinations of diclofenac sodium and misoprostol) for acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastrointestinal ulcers. The highest recommended daily dose of ARTHROTEC<sup>®</sup> 50 (50 mg of diclofenac sodium and 200 mcg of misoprostol; 3 times per day) would deliver 150 mg/day of diclofenac sodium and 600 mcg/day of misoprostol. The highest recommended daily dose of ARTHROTEC<sup>®</sup> 75 (75 mg of diclofenac sodium and 200 mcg of misoprostol; 2 times per day) would deliver 150 mg/day of diclofenac and 400 mcg/day of misoprostol.

In support of NDA 20-607, the sponsor submitted several preclinical studies of diclofenac:misoprostol combinations including pharmacology studies in mice and rats, acute oral toxicity studies in mice and rats, 4-week and 6-month oral toxicity studies in rats, 4-week oral toxicity study in dogs, 6-month oral toxicity study in monkeys, mutagenic studies (Ames test, forward mutations in Chinese hamster ovary cells, chromosomal aberrations in rat lymphocytes, mouse micronucleus assay), and a Segment II oral teratogenic study in rabbits. Pharmacology data were original; all other data had been

In preclinical pharmacological studies, it was shown that misoprostol inhibited diclofenac-induced gastric ulcers in rats; this directly supports the proposed marketing indication for ARTHROTEC<sup>®</sup> 50 and ARTHROTEC<sup>®</sup> 75. Moreover, diclofenac reduced the severity of adjuvant-induced arthritis in a rat model; diclofenac:misoprostol combinations produced similar reductions in severity. Thus, misoprostol did not alter the anti-inflammatory effects of diclofenac in this rat model. Furthermore, 100:1 and 10:1 diclofenac:misoprostol combination doses did not alter inhibition of carrageenan-induced paw edema in rats, compared to diclofenac alone.

In acute oral toxicity studies in mice; the minimum oral lethal dose of misoprostol in male and female mice was not determined (>20 mg/kg); clinical signs of toxicity were protraction and reduced motor activity. The minimum oral lethal dose of diclofenac was 50 mg/kg in males and females; clinical signs of toxicity were reduced motor activity, prostration and convulsions. The minimum oral lethal dose of the

misoprostol:diclofenac combination (2:500 ratio) was 0.4:100 mg/kg in males and 0.8:200 mg/kg in females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:375 ratio) was 0.53:100 mg/kg in males and 1.07:200 mg/kg in females. In combination studies, clinical signs of toxicity were reduced motor activity, prostration and convulsions. Thus, in mice, toxicity of misoprostol:diclofenac combinations was no greater than that of diclofenac alone; there was no significant difference between sexes.

In acute oral toxicity studies in rats; the minimum oral lethal dose of misoprostol in male and female rats was not determined (>20 mg/kg); clinical signs of toxicity were loose stools, prostration and reduced motor activity. The minimum oral lethal dose of diclofenac was 150 mg/kg in males and 100 mg/kg in females; clinical signs of toxicity were loose stools, prostration, reduced motor activity and arched back/standing hair. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:500 ratio) was 0.9:225 mg/kg in males and 0.4:50 mg/kg in females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:375 ratio) was 1.2:225 mg/kg in males and 0.27:50 mg/kg in females. In combination studies, clinical signs of toxicity were loose stools, prostration, reduced motor activity and arched back/standing hair. Thus, in rats, toxicity of misoprostol:diclofenac combinations was no greater than that of diclofenac alone; there was no significant difference between sexes.

In a 4-week oral toxicity study of diclofenac alone (0.5 and 6.0 mg/kg/day) and misoprostol:diclofenac combinations (0.002:0.5, 0.008:2.0 and 0.024:6.0 mg/kg/day) in the rat, the no effect dose of diclofenac alone was 0.5 mg/kg. The 6.0 mg/kg/day dose of diclofenac alone produced gastric lesions, atrophy/inflammation/fibrosis in the pancreas, and focal hepatic granulomas. The no effect dose of the misoprostol:diclofenac combination was 0.002:0.5 mg/kg/day. The toxicity and pharmacokinetics of orally administered diclofenac and diclofenac:misoprostol combinations did not differ in the rat.

In a 6-month oral toxicity study of diclofenac alone (1, 2.5 and 6 mg/kg/day) and misoprostol:diclofenac combinations (0.004:1, 0.01:2.5 and 0.024:6 mg/kg/day) in rats, the no effect dose of diclofenac alone was 1 mg/kg/day. The 2.5 mg/kg/day dose of diclofenac alone produced granular mucosal ulceration in the stomach, colonic lymphoid hyperplasia and uterine luminal distention; the 6 mg/kg/day dose of diclofenac alone produced granular mucosal ulceration in the stomach, extramedullary hematopoiesis in the spleen, mucosal ulceration, parietal granulation and mucosal hyperemia in the jejunum, colonic lymphoid hyperplasia, chronic myocarditis and myocardial necrosis in the heart, adenitis and sinusoidal edema/cystic spaces in mesenteric lymph nodes, uterine luminal distension and deaths

(3 females; 1 male and 1 female were sacrificed in extremis). The no effect dose of the misoprostol:diclofenac combination was 0.04:1 mg/kg/day). The toxicity and toxicokinetics of orally administered diclofenac and misoprostol:diclofenac combinations did not differ in rats. However, there was increased toxicity in the 6-month study compared to the 4-week study.

In a 4-week oral toxicity study of diclofenac alone (0.5 and 2.0 mg/kg/day) and misoprostol:diclofenac combinations (0.002:0.5, 0.004:1 and 0.008:2 mg/kg/day) in dogs, the minimal effect dose of diclofenac was 0.5 mg/kg/day. The 2.0 mg/kg/day dose of diclofenac alone produced renal papillary edema, renal papillary necrosis, extramedullary hematopoiesis of the spleen, thymic atrophy and deaths (1 male). The minimal effect dose of the misoprostol:diclofenac combination was 0.002:0.5 mg/kg/day. The toxicity and toxicokinetics of orally administered diclofenac and diclofenac:misoprostol combinations did not differ in the kidney, spleen and thymus. However, misoprostol:diclofenac combinations produced treatment-related prostrate hypoplasia, testicular oligospermia and absence of spermatozoa in the epididymis in males, while diclofenac alone only produced absence of spermatozoa in the epididymis. Reproductive organs of male dogs have been previously shown to be target organs of toxicity for misoprostol. Finally, there were no differences in toxicokinetics between diclofenac and diclofenac:misoprostol combinations.

In a 6-month oral toxicity study of diclofenac alone (6 and 50 mg/kg/day) and misoprostol:diclofenac combinations (0.024:6, 0.068:17 and 0.2:50 mg/kg/day) in monkeys, the no effect dose of diclofenac alone was 6 mg/kg/day. The 50 mg/kg/day dose of diclofenac alone produced mucosal ulceration/peritonitis of the stomach, duodenum and cecum, mucosal hemorrhage in the cecum, cortical dilation of the kidney, glomerulonephritis, peritonitis in the liver, lymphoid hyperplasia of the spleen, reactive hyperplasia/nonspecific lymphadenitis in the mesenteric lymph node and deaths (1 male and 2 females were sacrificed in extremis). The no effect dose of the misoprostol:diclofenac combination was 0.024:6 mg/kg/day. The toxicity and toxicokinetics of orally administered diclofenac and diclofenac:misoprostol combinations did not differ in monkeys.

In a Segment II oral teratogenic study of diclofenac alone (10, 30 and 100 mg/kg/day during days 6 through 18 of gestation) and misoprostol:diclofenac combinations (0.04:10, 0.12:30 and 0.4:100 mg/kg/day during days 6 through 18 of gestation) in rabbits, there were no treatment-related teratogenic effects.

Misoprostol:diclofenac combinations were negative in mutagenic studies (Ames test, forward mutations in Chinese hamster ovary cells, chromosomal aberrations in rat lymphocytes, mouse micronucleus assay).

In the safety assessment of ARTHROTEC<sup>®</sup>, the main issue is whether the toxicity and toxicokinetics of the proposed fixed combinations of diclofenac and misoprostol in the ARTHROTEC<sup>®</sup> formulations differ from those of either diclofenac or misoprostol alone. In the 4-week and 6-month oral toxicity studies in the rat and the 6-month oral toxicity study in the monkey, there were no differences in the toxicity and toxicokinetics between diclofenac and diclofenac:misoprostol combinations. In the 4-week oral toxicity study in the dog, the misoprostol component of the diclofenac:misoprostol combination produced toxicity in the reproductive organs of male dogs. However, there were no other differences in the toxicity between diclofenac:misoprostol combinations, and there were no differences in toxicokinetic parameters between diclofenac and diclofenac:misoprostol combinations in the dog. Thus, since the sponsor would use approved daily doses of diclofenac and misoprostol in the ARTHROTEC<sup>®</sup> formulations, the preclinical toxicity data suggest that the proposed clinical use of ARTHROTEC<sup>®</sup> would be reasonably safe.

One of the inactive ingredients in ARTHROTEC<sup>®</sup> 50 and ARTHROTEC<sup>®</sup> 75 is methacrylic acid copolymer (ARTHROTEC<sup>®</sup> 50 and ARTHROTEC<sup>®</sup> 75 tablets, respectively). Methacrylic acid copolymer is listed in the INACTIVE INGREDIENT GUIDE (January 1996) and is currently used in marketed drug products at concentrations Thus, the use of methacrylic acid copolymer in ARTHROTEC<sup>®</sup> 50 and ARTHROTEC<sup>®</sup> 75 tablets is reasonably safe.

It should be noted that the sponsor submitted a Segment II oral teratogenic study for the misoprostol:diclofenac combination in only 1 species; i.e., the rabbit. It is recommended that Segment II teratogenic studies be done in 2 species. Since the misoprostol component has an abortifacient property, it seems important to assess any interactive effect of misoprostol and diclofenac in a teratogenic study using a second species.

Finally, the reviewer has suggested a revised version for the Carcinogenesis, mutagenesis, impairment of fertility section, the Pregnancy section, and the Overdosage section of the labeling.

**RECOMMENDATIONS:**

From a preclinical viewpoint, the NDA application is approvable.

**APPEARS THIS WAY  
ON ORIGINAL**

**/S/**

8/9/96

Gerald A. Young Ph.D.  
Pharmacologist HFD-180

- cc: HFD-180
- HFD-181/CSO
- HFD-180/Dr. Choudary
- HFD-180/Dr. Fredd
- HFD-180/Dr. Young
- HFD-345/Dr. Viswanathan

**/S/**

8/9/96

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**APPEARS THIS WAY  
ON ORIGINAL**

M E M O R A N D U M

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

DATE: January 31, 1996

FROM: Pharmacology Team Leader  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180

SUBJECT: NDA 20,607 (Arthrotec) - Preclinical Deficiencies

TO: NDA 20,607

The following deficiencies are noted in this application.

1. The following reports of toxicology studies of the combination of diclofenac sodium and misoprostol are not included in this application but referred to NDA 19,268. The sponsor is inconsistent on inclusion of reports of combination drug studies in this application. For example, the report of Segment II. rabbit teratology study of the combination is included in this application and as well as NDA 19,268, but the following reports are not provided in this application:

a. Acute oral toxicity study of the association misoprostol/diclofenac compared to the toxicity of each component in the rat and the mouse.  
PSA-87F-0331/0332.

b. Four-week oral toxicity study of the combination of misoprostol/diclofenac in the rat.  
PSA-87F-0333.

c. Four-week toxicity study of the combination of misoprostol/diclofenac in the dog.  
PSA-87F-0334.

2. Report of a Segment II. teratology study in rats is not available. Sponsor was informed about this deficiency at the pre-NDA meeting. Only the report of a study in rabbits was included.

NDA 20-607  
Page 2

Sponsor should be asked to provide copies of the reports listed under 1.

**/S/**

**APPEARS THIS WAY  
ON ORIGINAL**

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Jasti B. Choudary, Ph.D., B.V.Sc.

cc:  
NDA 20,607  
HFD-180  
HFD-181/CSO  
HFD-180/Dr. Choudary  
HFD-180/Dr. Fredd  
HFD-180/Dr. Young

JBC/hw/1/31/96

C:\WPFILES\PHARM\N\20607601 **APPEARS THIS WAY  
ON ORIGINAL**

# Incidence of Adverse Events Causing Withdrawal in Phase III Fixed Combination Trials

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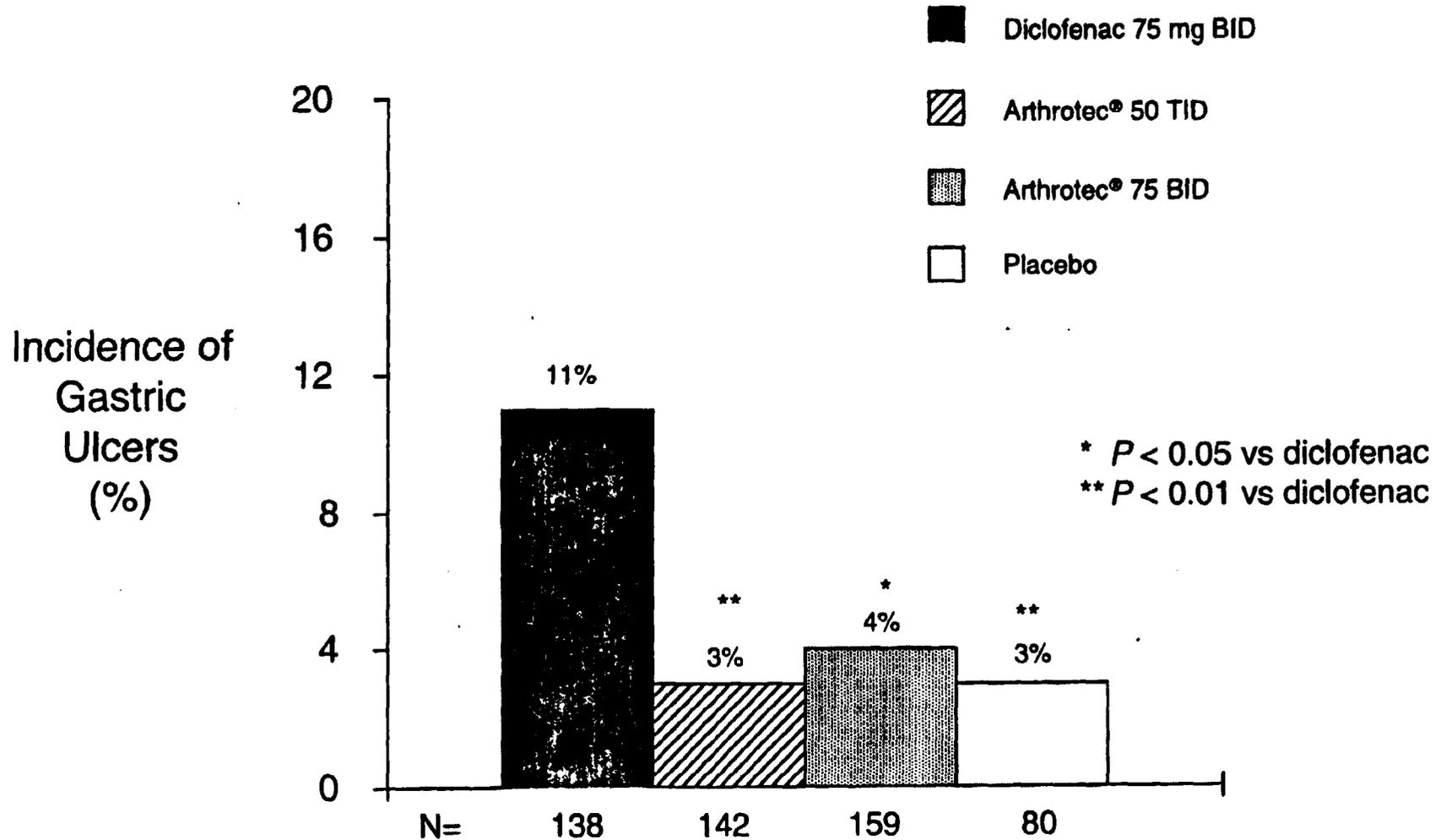
	Arthrotec®		Diclofenac		Placebo	
	%	(N)	%	(N)	%	(N)
	100.0	(2184)	100.0	(1691)	100.0	(146)
Withdrawn due to adverse event	11.2		8.2		4.1	
Abdominal Pain	4.6		3.0		2.1	
Diarrhea	3.2		1.1		0.7	
Nausea	2.1		1.6		0.7	
Dyspepsia	1.3		1.2		0.0	
Flatulence	1.1		0.3		0.0	

# Arthrotec®

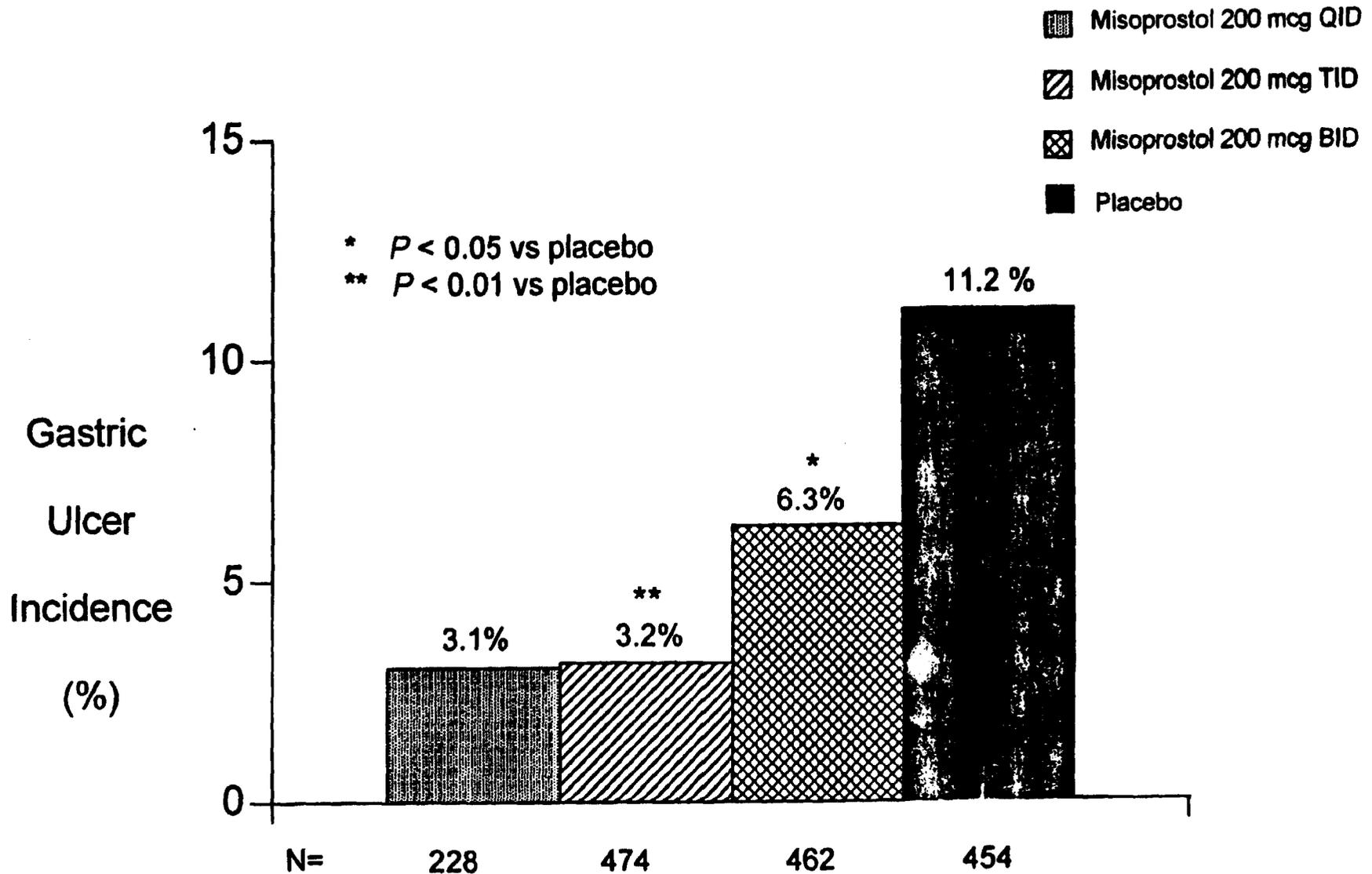
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- Misoprostol protects against diclofenac-induced GU
- Two adequate and well controlled studies support the improved GU safety of Arthrotec at BID and TID dosing
  - 349 study
  - 053 study

Incidence of Gastric Ulcers ( $\geq 3$  mm) in Patients Treated with Diclofenac and  
Diclofenac/Misoprostol  
(Study NN2-94-02-349)



**Incidence of NSAID-Induced Gastric Ulcers ( $\geq 3$  mm) in Patients Treated with  
Misoprostol 200 mcg BID-QID (12 Weeks)  
(Study S81-89-02-053)**



N= Various NSAIDs were allowed

# Arthrotec®

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## Conclusions

- Misoprostol does not interfere with the anti-arthritic properties of diclofenac in OA and RA
- Arthrotec is associated with a lower incidence of GU than diclofenac
- Safety profile of Arthrotec® is well defined

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020607**

**STATISTICAL REVIEW(S)**

18 years or older satisfying the ARA criteria (for RA) or ACR criteria (for OA), and a functional capacity classification of I-III and requiring NSAID therapy would be qualified. Patients excluded were those with known or suspected active peptic ulceration or gastrointestinal bleeding and other conditions which might preclude the use of an NSAID. The primary efficacy variables were Physician's and Patient's Global Assessments (5-point scale, very good to very poor). The secondary efficacy variables were Duration of Morning Stiffness, Assessment of Night Pain (4-point scale) for both RA and OA patients (baseline, weeks 4, 8, and 12) and Health Assessment questionnaires (HAQ) (RA only) or Osteoarthritis Severity Index (OA only) at baseline and end of study.

## **Statistical Methods**

### **Protocol Method of Analysis**

The protocol identifies two patient populations, the Intent-to-Treat (ITT) which includes all patients who had taken any study medication and the Protocol Evaluable Patients which is a subset of the ITT population by excluding those who violated any significant inclusion or exclusion criteria. All assessments of arthritic condition, except duration of morning stiffness, will generate ordered categorical data which will be analyzed by logistic regression. The model for the analysis will, if necessary, include other factors correlated with outcome, such as age, sex, site, country, duration of treatment, tablet consumption and concomitant medication. If the variable duration of morning stiffness is approximately normally distributed, it will be analyzed by analysis of variance; otherwise, it too will be reduced to an ordered categorical response.

### **Sponsor's Deviation in Method of Analysis**

All randomized patients were included in the ITT analysis without excluding those who took no medication or who were found to be ineligible after admission, since there were only three such patients in each of these two categories.

Last observation carried forward (LOCF) was used in the ITT analysis instead of the protocol method of assigning the worst score because some patients deteriorated by only one grade and withdrew.

Because there was some imbalance in the arthritis assessments of patients between the two treatment groups at baseline, particularly among RA patients, analyses of global assessments and night pain were based on changes from baseline

rather than absolute score at each follow-up visit. Morning stiffness data were also reduced to categorical data and analyzed by logistic regression. Demographic variables, duration of treatment, tablet consumption and concomitant medication were included as potential covariates in the logistic regression analyses.

### Results of the Study

Fifty-one (51) investigators in 10 countries participated in this study. Only 10 investigators enrolled 10 or more patients. A total of 253 patients was randomized to Arthrotec 75 and 261 patients to diclofenac 75 mg SR. The disposition of the patients is shown in the table below by RA and OA.

**Reasons for Dropouts by RA and OA**

	Arthrotec 75	Diclofenac 75 mg SR	Overall
<b>RA patients</b>			
Completed	102 (69.9%)	105 (67.7%)	207 (68.8%)
Lost to follow-up	1 ( 0.7%)	0 ( 0)	1 ( 0.3%)
Dropouts	43 (29.5%)	50 (32.3%)	93 (30.9%)
Protocol violation	7 ( 4.8%)	7 ( 4.5%)	14 ( 4.7%)
Treatment failure	5 (3.4%)	7 ( 4.5%)	12 ( 4.0%)
Adverse events	31 (21.2%)	36 (23.2%)	67 (22.3%)
<b>Total</b>	146 (100.0%)	155 (100.0%)	301 (100.0%)
<b>OA patients</b>			
Completed	75 (70.1%)	79 (74.5%)	154 (72.3%)
Lost to follow-up	1 ( 0.9%)	4 ( 3.8%)	5 ( 2.3%)
Dropouts	31 (29.0%)	23 (21.7%)	54 (25.4%)
Protocol violation	6 ( 5.6%)	4 ( 3.8%)	10 ( 4.7%)
Treatment failure	3 (2.8%)	0 (0)	3 ( 1.4%)
Adverse events	22 (20.6%)	19 (17.9)	41 (19.2%)
<b>Total</b>	107 (100.0%)	106 (100.0%)	213 (100.0%)

The demographics were well balanced between treatments. The mean age was 59 years and slightly over two-thirds (Overall 68.7%; RA 65.8% vs. OA 72.8%) of the patients were females. Fifty-nine percent (59%) of the patients had RA and 42% had OA. Three patients had both RA and OA and were considered as RA patients for the purpose of the analysis. The mean duration of disease was 9.2 years for Arthrotec patients and 7.9 years for diclofenac patients. The average number of joints affected was 11 in both treatments.

## RA Patients

The baseline global assessments were imbalanced with a greater percentage of patients with a **Very Good** assessment in the diclofenac 75 mg SR group than in the Arthrotec group. The other efficacy variables were generally comparable between the treatment groups.

	P-val	Arthrotec 75		Diclofenac 75 mg SR	
<b>Physician's Global</b>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (3.4)		3 (1.9)
Very Good		1 (0.7)	17 (11.6)	11 (7.1)	13 (8.4)
Good		47 (32.2)	55 (37.7)	47 (30.3)	64 (41.3)
Fair	.139	74 (50.7)	48 (32.9)	76 (49.0)	56 (36.1)
Poor		21 (14.4)	20 (13.7)	20 (12.9)	17 (11.0)
Very Poor		3 (2.1)	1 (0.7)	1 (0.6)	2 (1.3)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
<b>Patient's Global</b>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			4 (2.7)		3 (1.9)
Very Good		4 (2.7)	12 (8.2)	10 (6.5)	14 (9.0)
Good		37 (25.3)	50 (34.2)	42 (27.1)	65 (41.9)
Fair	.986	74 (50.7)	48 (32.9)	74 (47.7)	43 (27.7)
Poor		25 (17.1)	25 (17.1)	25 (16.1)	26 (16.8)
Very Poor		6 (4.1)	7 (4.8)	4 (2.6)	4 (2.6)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
<b>Night Pain</b>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			4 (2.7)		4 (2.6)
Not Bothered		40 (27.4)	54 (37.0)	51 (32.9)	72 (46.5)
Bothered a Little	.286	58 (39.7)	43 (29.5)	47 (30.3)	45 (29.0)
Bothered a Lot		42 (28.8)	40 (27.4)	54 (34.8)	26 (16.8)
Bothered Terribly		6 (4.1)	5 (3.4)	3 (1.9)	8 (5.2)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
<b>Morning Stiffness (min)</b>		N mean (SE)		N mean (SE)	
Baseline		145	88.3 (7.04)	154	78.2 (6.52)
Final	NA	142	69.9 (6.00)	150	63.2 (7.21)
<b>Health Assess. Questionnaire</b>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown		1 (0.7)	8 (5.5)	2 (1.3)	13 (8.4)
0 - 10		48 (32.9)	56 (38.4)	54 (34.8)	69 (44.5)
11 - 20		43 (29.5)	35 (24.0)	56 (36.1)	34 (21.9)
21 - 30	.790	28 (19.2)	21 (14.4)	27 (17.4)	24 (15.5)
31 - 40		22 (15.1)	23 (15.8)	13 (8.4)	13 (8.4)
41 - 50		4 (2.7)	3 (2.1)	3 (1.9)	2 (1.3)
Total		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)

OA Patients

Baseline of the various efficacy variables was generally balanced between the two treatments with a slightly poorer rating in the Arthrotec group than in the diclofenac group.

	P-val	Arthrotec 75		Diclofenac 75 mg SR	
<u>Physician's Global</u>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (4.7)		6 (5.7)
Very Good		4 (3.7)	13 (12.1)	2 (1.9)	14 (13.2)
Good	.537	33 (30.8)	43 (40.2)	29 (27.4)	44 (41.5)
Fair		54 (50.5)	32 (29.9)	59 (55.5)	28 (26.4)
Poor		15 (14.0)	13 (12.1)	16 (15.1)	14 (13.2)
Very Poor		1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
<u>Patient's Global</u>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (4.7)		6 (5.7)
Very Good		5 (4.7)	15 (14.0)	3 (2.8)	17 (16.0)
Good	.690	29 (27.1)	36 (33.6)	29 (27.4)	33 (31.1)
Fair		49 (45.8)	33 (30.8)	47 (44.3)	33 (31.1)
Poor		20 (18.7)	16 (15.0)	25 (23.6)	13 (12.3)
Very Poor		4 (3.7)	2 (1.9)	2 (1.9)	4 (3.8)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
<u>Night Pain</u>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			6 (5.6)		6 (5.7)
Not Bothered		24 (22.4)	40 (37.4)	19 (17.9)	43 (40.6)
Bothered a Little	.233	43 (40.2)	36 (33.6)	44 (41.5)	39 (36.8)
Bothered a Lot		30 (28.0)	22 (20.6)	32 (30.2)	13 (12.3)
Bothered Terribly		10 (9.3)	3 (2.8)	11 (10.4)	5 (4.7)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
<u>Morning Stiffness (min)</u>		N mean (SE)		N mean (SE)	
Baseline	NA	107	30.5 (4.41)	104	38.2 (5.73)
Final		101	24.3 (4.22)	98	26.4 (5.40)
<u>OA Sev. Index</u>		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			9 (8.4)	2 (1.9)	9 (8.5)
0 - 5		7 (6.5)	18 (16.8)	5 (4.7)	16 (15.1)
6 - 10		32 (29.9)	35 (32.7)	24 (22.6)	34 (32.1)
11 - 15	.187	56 (52.3)	33 (30.8)	63 (59.4)	40 (37.7)
16 - 20		11 (10.3)	11 (10.3)	12 (11.3)	7 (6.6)
> 20		1 (0.9)	1 (0.9)		
Total		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)

The tables above are the summary statistics of the efficacy variables at baseline and the final visit. The p-values are the differences between the two treatment groups using the change from baseline method which categorizes patients into several categories - Improved by at least 2 grades, Improved by 1 grade, No change, Worsened by 1 grade, and Worsened by at least 2 grades. The p-value for Morning Stiffness was not provided by the sponsor except that it was stated that there was no statistically significant difference. Note that the p-values were derived from logistic regression analyses with a number of covariates but the details of the models and output of the analyses were not provided.

### III. Reviewer's Comment

This was the first study to compare Arthrotec with the diclofenac slow release formulation in OA and RA patients. Previous studies all compared Arthrotec with the enteric coated diclofenac sodium. There are several design flaws that make the study results difficult to interpret though on surface, the efficacy of Arthrotec 75 and diclofenac 75 mg SR looked alike in the study population. The following is a list of deficiencies in its study design.

1. There was no placebo controlled group in the study. This raises the question of internal validity of the study especially in view of the results from a previous U.S. RA study (NN2-94-02-352: see statistical review dated 9/24/96) in which Arthrotec could not be distinguished from placebo in many study centers.
2. The set of efficacy variables used was different from what we used to see, especially in RA studies. Of the four primary efficacy variables that FDA used in evaluating RA efficacy, only the two global measurements (Physician's and Patient's) were employed in this study. The two objective measurements, number of painful joints and number of swollen joints were not measured. Instead, the night pain, morning stiffness, and the Health Assessments Questionnaire (HAQ) were used. We have no experience in these other 3 variables regarding their sensitivity in efficacy measurement. It is less a problem in the OA subpopulation. The three primary efficacy variables that FDA used in the OA evaluation are the Physician's Global Assessment, Patient's Global Assessment, and a variable that measures pain. In this study, besides the two global assessments, there was the OA severity index which served as a pain measurement.
3. The study was not a truly double-blind study. The Arthrotec 75 and diclofenac 75 mg SR tablets are different in appearance. The blinding was achieved by packaging all tablets in identical

foil strips. Thus, when a patient opened a package, the identity of the drug would be disclosed to the patient.

4. The study design did not include a flare at baseline. Patients had already been maintained a stable disease condition when they entered into the study. Thus, there was very little difference in each of the efficacy measures between baseline and the end of the study. It is not known what proportion of patients would need treatment during the 12-week study period and what proportion of patients would have spontaneous remission. Because of the *no flare* design, the Q-analysis was not done and could not have been meaningfully interpreted anyway. The Q-statistic is the ratio of the mean improvement from baseline between the test drug and the active control. The lower bound of the 95% confidence interval of Q is used to decide whether the test drug is at least as good as the control. If the mean improvement of either the test or the control drug is not significantly different from zero as in the present situation, the 95% confidence interval of Q would fail to exist. The sponsor had tried to circumvent this situation in previous non-U.S. studies with the *no flare* design by using the mean score at a final visit instead of the mean improvement score in the Q-analysis (see previous statistical review dated 9/23/96). However, as pointed out by this reviewer, we have no experience in evaluating this alternative approach.

5. One of the protocol amendments allowed patients to use concomitant analgesics. Other than the statement by the sponsor that concomitant medications would be used as a covariate in the logistic regression analysis, no details are provided as to the impact of the concomitant analgesics. The use of concomitant analgesics usually blurs the difference between treatment groups.

#### IV. Conclusions

This non-U.S. study of mixed OA and RA patients compared Arthrotec 75 bid to diclofenac 75 mg SR bid. The deficiencies of the design include the lack of placebo control, the method of blinding (patients were not blinded), the lack of objective measures (number of painful joints and number of swollen joints) in RA efficacy assessments, the lack of the flare condition at baseline and the absence in the evaluation of the impacts of concomitant analgesics. These undesirable features of the study design do not provide convincing statistical evidence that the two drugs are comparable in efficacy.

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/S/

Hoi M. Leung, Ph.D.<sup>U</sup>  
Mathematical Statistician

Concur:

/S/

Ralph Harkins, Ph.D.  
Director, Division of Biometrics IV

Archive: NDA 20-607

cc:

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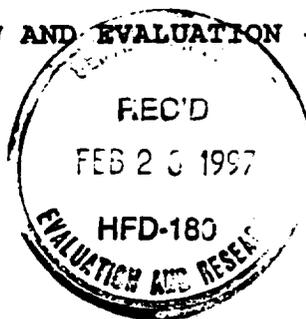
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STATISTICAL REVIEW AND EVALUATION --- NDA



Date: FEB 18 1997

NDA #: 20-607

Applicant: G. D. Searle & Co.

Name of Drug: Arthrotec (Diclofenac sodium/misoprostol)  
50 mg/200 mcg / 75 mg/200 mcg Tablets

Indication: Treatment of sign and symptoms of osteoarthritis  
and rheumatoid arthritis

Documents Reviewed: NDA Supplemental Vol. 1-4 (Study 013) Dated  
December 17, 1996

Medical Reviewer: This review has been discussed with the medical  
officer, Kathy Robie-Suh, M.D., Ph.D. (HFD-180)

Key Words: Ulceration, Intent-to-Treat, ulcer size

**A. Background**

Arthrotec tablets are a fixed combination of either 50 mg  
diclofenac sodium/200 mcg misoprostol (Arthrotec 50) or 75 mg  
diclofenac sodium/200 mcg misoprostol (Arthrotec 75).

In the current NDA, the sponsor seeks approval of Arthrotec for  
acute and chronic treatment of the signs and symptoms of  
osteoarthritis and rheumatoid arthritis in patients at risk of  
developing NSAID-induced gastroduodenal ulcers.

In support of this claim, the sponsor had submitted seven pivotal  
studies in December 26, 1995. These studies had been reviewed and  
documented in Statistical Review and Evaluation --- NDA dated  
September 11, 1996.

Among seven pivotal studies, it was found that the six-week,  
placebo-controlled OA study (protocol 349), which enrolled only  
patients with a history of UGI ulcer or erosive disease, provided  
support of the efficacy of the Arthrotec 50 TID over diclofenac  
75 mg BID and also provided some evidence of efficacy of the  
Arthrotec 75 BID over diclofenac 75 mg BID for prevention of

developing NSAID-induced gastric ulcer for OA patients.

However, for prevention of developing NSAID-induced duodenal ulcer for OA patients, study 349 failed to support the efficacy of either the Arthrotec 50 TID or the Arthrotec 75 BID over diclofenac 75 mg BID.

There is a need of another study which replicates the results of study 349 regarding gastric lesion incidence.

The sponsor has submitted the report for Arthrotec study 013 to provide this replication.

This reviewer will address the efficacy and safety of Arthrotec regarding gastroduodenal damage in this review.

#### **B. Study I88-94-02-013**

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

This was a randomized, double-blind, parallel group, multicenter (51 investigators) study comparing Arthrotec 75 and diclofenac 75 mg slow release (SR), administered twice daily for 12 weeks in the treatment of patients with rheumatoid arthritis or osteoarthritis.

Randomization was stratified for rheumatoid arthritis (RA) and osteoarthritis (OA) patients to ensure equivalent numbers of patients with RA in each treatment group and equivalent numbers of patients with OA in each treatment group.

Separate randomizations were used for patients with RA or OA and patients were randomized in blocks of six for each center.

The primary objective of the study was to compare the antiarthritic efficacy and the gastroduodenal mucosal damage associated with Arthrotec 75 BID and diclofenac 75 mg SR BID in patients with either rheumatoid arthritis or osteoarthritis.

This was one of the first major endoscopic studies in which endoscopic examination had been employed solely at the end of the study, thereby mimicking clinical practice in that a proportion of the patients enrolled would almost certainly have had pre-

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existing ulceration and were not excluded from the study.

A single endoscopic examination of mucosa of stomach and duodenum was performed at final follow-up. Numbers of petechiae, erosions, ulcers and presence of intramucosal or intraluminal blood was recorded.

An erosion was defined as a lesion producing a definite break in the mucosa but without depth. An ulcer was defined as any lesion with unequivocal depth, regardless of size.

The primary response variable was the proportion of patients with a gastroduodenal ulcer, and the significance of treatment differences were assessed by Fisher's exact test. In addition, gastric and duodenal ulceration rates were assessed separately and tested in the same way.

Erosive lesions in the stomach and duodenum were assigned the following scores:

Erosive lesions	0	none
	1	1-3 erosions
	2	4-10 erosions
	3	>10 erosions
	4	ulcer

If patients failed to undergo endoscopy at their final visit, they were excluded from analyses of endoscopically determined results. However, if they cited a serious gastrointestinal event (perforation, ulceration or bleeding) as a reason for withdrawal, they were assigned the worst possible outcome for that response and included in the analyses.

Power calculations were carried out for two primary response variables - the gastroduodenal ulceration rate and the Global Assessment of Arthritic Condition. This study required two hundred patients per treatment group with a known endoscopic outcome. That sample size provided 80% power to detect the expected treatment difference (4% ulceration Arthrotec; 11% diclofenac) with one-sided tests carried out at the 5% level of significance.

This was on the basis that a previous study had shown an

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## Statistical Review and Evaluation (Amended Review #2)

NDA 20-607 (Related:IND 32,708)

Name of Drug : Arthrotec (diclofenac sodium/misoprostol)

Applicant : G. D. Searle & Co.

Indication : *For the temporary relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankelosing spondilitis*

Dosage : Arthrotec I (diclofenac 50 mg/misoprostol 200 mcg) b.i.d. or t.i.d.

Arthrotec II (diclofenac 75 mg/misoprostol 200 mcg) b.i.d.

Documents Reviewed: Volumes 1-4 dated 12/17/96 of NDA 20-607.

Reviewer : Hoi M. Leung, Ph.D.

Previous Statistical Reviews Dated: 9/23/96 and .11/27/96

Date Completed: 3/10/97

MAR 10 1997



### I. Background

This latest submission is a study report to which the sponsor wants to cross-reference to NDA 20-607. The study protocol is identified as I88-94-02-013. This was a multicenter, multinational, randomized, double blind, parallel group comparison of Arthrotec 75 (diclofenac sodium 75 mg and misoprostol 200 mcg) and diclofenac 75 mg slow release, administered twice daily in patients with rheumatoid arthritis or osteoarthritis. The duration of the treatment period was 12 weeks. This was the first study which compared Arthrotec with the slow release formulation of diclofenac. Previous studies of Arthrotec compared with the enteric coated formulation of diclofenac. This review will only address the efficacy portion of the study. The statistical aspects of the ulcer incidences and other adverse events of this study will be addressed by the reviewing statistician who directly supports HFD-180.

### II. Study Description (Protocol I88-94-02-013)

The primary objective of the study was to compare the anti-arthritic efficacy and the upper gastrointestinal safety (as assessed by endoscopy) of Arthrotec 75 BID and diclofenac 75 mg SR BID in the treatment of patients with rheumatoid arthritis (RA) or osteoarthritis (OA). The secondary objectives were to compare the tolerability of the two treatments for various adverse events. Endoscopy was only performed at the end of the study but not before.

Randomization was stratified by type of arthritis (RA or OA) and by center with a block size of six. Blinding was achieved by foil/foil packing of the study drug supplies and return of unused medication to a third party for tablet-return counts. Patients

ulceration rate of approximately 11% on diclofenac and 4% on diclofenac/misoprostol (Arthrotec). It was assumed that Arthrotec 75 mg would not cause more ulcers than diclofenac 75 mg SR, and that one-sided significance testing would therefore be appropriate.

To attain the required number of 200 patients per treatment group with known endoscopic outcomes it was assumed, based on experience of earlier studies, that there was a 20% drop-out rate. Consequently, it was projected to enroll 500 patients.

The design of this study using a sample size 200 per treatment group provided 80% power to detect a difference between 50% on one treatment and 35.8% (or 64.2%) on the other for Physician's or Patient's Global Assessments, using two-sided tests carried out at the 5% level of significance.

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

A total of 514 patients were enrolled into study, which was conducted by 51 European investigators. Two hundred fifty-three (253) were randomized to received Arthrotec 75 and 261 to receive diclofenac 75 mg SR.

The proportion of withdrawals were very similar in the two treatment groups, 29% (74) on Arthrotec 75 and 28% (73) on diclofenac 75 mg SR.

### **2.1 Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 1.

As seen from Table 1, there were no statistically significant differences between the treatment groups with respect to age, gender, and type of arthritis and disease duration.

Comparisons of baseline assessments of arthritis status showed no significant treatment group differences in the physician's and patient's global assessment.

There was slightly greater proportion of patients on Arthrotec 75 with a history of prior gastroduodenal ulceration or upper

gastrointestinal hemorrhage (14.3 vs 10.3 on diclofenac 75 mg SR). In addition, there was a greater percentage of patients particularly with RA, with a global assessment of arthritic condition designated as 'very good' on admission in the diclofenac 75 mg SR group (for physicians' global assessment, 7.1% for diclofenac 75 mg SR vs 0.7% for Arthrotec 75).

For the patients who did not undergo endoscopy, the time spent on study medication was the same in both treatment groups and there was no evidence to suggest that there was any selection bias between groups.

## 2.2 Sponsor's Analysis of Endoscopy Data

There were 210 patients on Arthrotec 75 and 216 on diclofenac 75 mg SR who underwent the an endoscopic evaluation at final follow-up.

The results of the final gastric endoscopy scores and final duodenal endoscopy scores for all patients who underwent final endoscopy are given below.

**Protocol I88-94-02-013**  
**Number of Patients with Erosive Lesion at Final Endoscopy**

	Number of Patients (%)			
	Final Gastric Endoscopy		Final Duodenal Endoscopy	
	Arthrotec 75 7444 (N=210)	Diclofenac 75 mg SR (N=216)	Arthrotec 75 (N=209)	Diclofenac 75 mg SR (N=215)
None	177 (84%)	124 (57%)	193 (92%)	181 (84%)
1-3 Erosion	15 ( 7%)	31 (14%)	9 ( 4%)	9 ( 4%)
4-10 Erosion	5 ( 2%)	14 ( 7%)	3 ( 1%)	6 ( 3%)
>10 Erosion	2 ( 1%)	15 ( 7%)	0 ( 0%)	5 ( 2%)
Ulcer	11 ( 5%)	32 (15%)	4 ( 2%)	14 ( 7%)

Copied from Table 15, I88-96-06-013, page 52.

**P-values for Treatment Comparison --- Protocol I88-94-02-013**

Treatment Comparison	Final Gastric Endoscopy	Final Duodenal Endoscopy
With an ulcer	0.001	0.028

Fisher's exact test

Ulcers were defined as all lesions with unequivocal depth on the basis that even small lesions could be of full thickness leading to bleeds and/or perforation.

With regard to erosive damage, gastroduodenal ulceration, the primary endpoint, occurred in 6.7 % of the Arthrotec 75 group compared with 19.4% on diclofenac 75 mg SR (p=0.001). The differences in ulceration rate for the stomach and the duodenum separately were also statistically significant (see table above).

However, many previous studies have taken a cut-off of  $\geq 5$ mm as the criterion for ulceration. Results of gastric ulceration and duodenal ulceration when ulcers were defined as  $\geq 5$ mm are given below.

**Protocol I88-94-02-013**

**Gastric Ulceration Rate When Ulcers were defined as  $\geq 5$ mm**

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	9/210 ( 4%)	0.003
Diclofenac 75 mg SR	26/216 (12%)	

Fisher's exact test

**Protocol I88-94-02-013**

**Duodenal Ulceration Rate When Ulcers were defined as  $\geq 5$ mm**

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	3/209 ( 1%)	0.031
Diclofenac 75 mg SR	11/215 ( 5%)	

Fisher's exact test

As seen from the table above, when ulcers were defined as  $\geq 5$ mm, the differences in ulceration rate for the stomach and the

duodenum separately were also statistically significant.

The main drug-related adverse events were GI in nature. Withdrawals rates for abdominal pain and diarrhea were lower on Arthrotec 75 than diclofenac 75 mg SR. Withdrawals for nausea, vomiting, dyspepsia and flatulence were higher on Arthrotec 75 than diclofenac 75 mg SR.

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

#### **3.1 Reviewer's Comments on Study Design**

The design of this study was different from that of study 349. In study 349, patient must demonstrate an OA flare and have a prior documented history of a gastric, pyloric channel or duodenal ulcer, or greater than ten erosions in the stomach or greater than ten erosions in the duodenum to be eligible for enrollment. However, the patient must not have an esophageal, gastric, pyloric channel or duodenal ulcer or more than ten erosions in the stomach or duodenum.

In this study, endoscopic examination had been employed solely at the end of the study, thereby mimicking clinical practice in that a proportion of the patients enrolled would almost certainly have had pre-existing ulceration and were not excluded from the study.

#### **3.2 Reviewer's Comments on Randomization**

The sponsor did not submit the predetermined randomization sequence code and actual treatment assignment. Randomization could not be evaluated. But as seen from the sponsor's listing of enrollment by investigator and treatment, patients were well allocated between treatment groups with maximum difference of two patients.

#### **3.3 Lack of Baseline Endoscopic Evaluation**

Due to lack of baseline endoscopic evaluation, it was unknown whether there was statistically significant differences among the treatment groups with respect to baseline gastric and duodenal endoscopy score.

Sponsor's efficacy analysis was based on the assumption that two treatment groups were comparable with respect to gastric and duodenal endoscopy score at baseline. But, this assumption might not be true and could not be verified. This might cast doubt about the results of efficacy analysis. The results could be biased in favor of the Arthrotec due to baseline imbalance.

However, for prevention of developing NSAID-induced gastric ulcer, in view of small p-value ( $p=0.001$ ), the baseline imbalance in gastric endoscopy score if existed might have negligible effect on the efficacy results in terms of significance.

### 3.4 Reviewer's Comments on Primary Endpoint

In this study, the primary endpoint measured the ulceration rate instead of ulcer incidence rate. The primary endpoint measured in this study was different from that in study 349.

The sponsor's analysis was not an Intent-to-Treat analysis but an evaluable analysis. It did not include all randomized patients but included 210 patients in the Arthrotec 75 group and 216 in the diclofenac 75 mg SR group who underwent the an endoscopic evaluation at final follow-up.

The results of the final gastric endoscopy scores and final duodenal endoscopy scores for an Intent-to-Treat analysis are given below.

**Protocol I88-94-02-013**  
**Number of Patients with Erosive Lesion at Final Endoscopy**  
**Intent-to-Treated Analysis**

	Number of Patients (%)			
	Final Gastric Endoscopy		Final Duodenal Endoscopy	
	Arthrotec 75 (N=253)	Diclofenac 75 mg SR (N=261)	Arthrotec 75 (N=252)	Diclofenac 75 mg SR (N=261)

Unknown	43 (17%)	45 (17%)	44 (17%)	46 (19%)
None	177 (70%)	124 (48%)	192 (76%)	181 (69%)
1-3 Erosion	15 (6%)	31 (12%)	9 (4%)	9 (3%)
4-10 Erosion	5 (2%)	14 (5%)	3 (1%)	6 (2%)
>10 Erosion	2 (1%)	15 (6%)	0 (0%)	5 (2%)
Ulcer	11 (4%)	32 (12%)	4 (2%)	14 (5%)

Copied from Table 15, I88-96-06-013, page 52.

**P-values for Treatment Comparison --- Protocol I88-94-02-013**

Treatment Comparison	Final Gastric Endoscopy	Final Duodenal Endoscopy
With an ulcer	0.001	0.028

Fisher's exact test

As seen from the table above, the findings in the Intent-to-Treat analysis were similar to those given by the sponsor in terms of significance.

The results of Intent-to-Treat analyses of gastric ulcer and duodenal ulcer when ulcers were defined as  $\geq 5\text{mm}$  are given below.

**Protocol I88-94-02-013  
Gastric Ulceration Rate When Ulcers were defined as  $\geq 5\text{mm}$   
Intent-to-Treat Analysis**

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	9/253 (4%)	0.005
Diclofenac 75 mg SR	26/261 (10%)	

Fisher's exact test

**Protocol I88-94-02-013  
Duodenal Ulceration Rate When Ulcers were defined as  $\geq 5\text{mm}$   
Intent-to-Treat Analysis**

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	3/253 (1%)	0.054
Diclofenac 75 mg SR	11/261 (4%)	

Fisher's exact test

As seen from the table above, when ulcers were defined as  $\geq 5$ mm, the findings in the Intent-to-Treat analysis were similar to those given by the sponsor in terms of significance for gastric ulcer. For duodenal ulcer, contrary to sponsor's finding, the results of ITT analysis revealed that Arthrotec 75 BID was statistically marginally significantly different from diclofenac 75 mg SR BID ( $p=0.054$ ).

### 3.5 Gastric Ulceration and Duodenal Ulceration Rates by Patient

This reviewer performed an analysis of ulceration rate for gastric ulcer and duodenal ulcer for OA patients and RA patients. The results are given below.

Protocol I88-94-02-013  
Number of Patients with Gastric Ulcer by Patient  
Intent-to-Treat Analysis

Patient	Arthrotec 75 BID	Diclofenac 75 mg SR BID	Between Treatment p-value <sup>1</sup>	CMH p-value <sup>2</sup>
Osteoarthritis	2/107 (1.9%)	15/106 (14.2%)	<0.001	<0.001
Rheumatoid arthritis	9/146 (6.2%)	17/155 (11.0%)	0.153	

<sup>1</sup>Fisher's Exact test

<sup>2</sup>Cochran-Mantel-Haenszel statistics controlling for strata

Protocol I88-94-02-013  
Number of Patients with Duodenal Ulcer by Patient  
Intent-to-Treat Analysis

Patient	Arthrotec 75 BID	Diclofenac 75 mg SR BID	Between Treatment p-value <sup>1</sup>	CMH p-value <sup>2</sup>
Osteoarthritis	1/107 (0.9%)	8/106 (7.5%)	0.019	0.019
Rheumatoid arthritis	3/146 (2.1%)	6/155 (3.9%)	0.503	

<sup>1</sup>Fisher's Exact test

<sup>2</sup>Cochran-Mantel-Haenszel statistics controlling for strata

As seen from the tables above, for OA patients, the Arthrotec 75 BID was statistically significantly different from diclofenac 75 mg SR BID for both gastric ulcer and duodenal ulcer. But, for RA patients, there was no treatment difference for both gastric

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ulcer and duodenal ulcer; treatment differences were small.

### 3.6 Sensitivity Analysis on Duodenal Ulcer

For prevention developing NSAID-induced of duodenal ulcer, this reviewer did the following sensitivity analysis to find out how many alternations in ulceration status would change the 2-sided p-value from the observed p-value to greater than 0.05, keeping sample sizes fixed. The results for study 013 are given in Table 2.

- (1) In case 1, the Arthrotec 75 ulceration rate was varied, keeping the diclofenac 75 mg SR ulceration rate fixed at 5.4%.
- (2) In case 2, the diclofenac 75 mg SR ulceration rate was varied, keeping the Arthrotec 75 ulceration rate fixed at 1.6%.
- (3) In case 3, both Arthrotec 75 and Diclofenac 75 mg SR ulceration rates were varied.

Case 1 results indicates that a change of 0.4% from the observed Arthrotec rate of 1.6%, changes the 2-sided p-value (by Fisher's Exact test) from (greater 5%). This difference of 0.4% is numerically equivalent to 1 ulcerated Arthrotec patient in the numerator of the ulceration rate when given that the sizes of the Arthrotec and diclofenac 75 mg SR are 253 and 261, respectively, and the diclofenac ulceration rate is 5.4%.

Case 2 results indicates that a change of 0.8% from the observed Diclofenac rate of 5.4%, changes the 2-sided p-value (by Fisher's Exact test) from (greater 5%). This difference of 0.8% is numerically equivalent to 2 ulcerated diclofenac patients in the numerator of the ulceration rate when given that the sizes of the Arthrotec and diclofenac 75 mg SR are 253 and 261, respectively, and the Arthrotec ulceration rate is 1.6%.

Case 1 and 2 results also indicate that alternations in the ulceration status of 1 patient in the Arthrotec group or 2 patients in the diclofenac group (i.e. from non-ulcerated to

ulcerated in the Arthrotec group or from ulcerated to non-ulcerated in the diclofenac group) could change the observed 2-sided p-value 0.028 to greater than 0.05.

Case 3 results indicate that a change in the status of just a change of 1 Arthrotec patient from non-ulcerated to ulcerated, when there was a change of 1 diclofenac patient from ulcerated to non-ulcerated would cause a shift in the 2-sided p-value from 0.028 to a p-value of greater than 0.05.

### **C. Overall Summary and Recommendation**

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

Study 013 provide some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer for OA patients.

However, due to lack of baseline endoscopic evaluation and different study design from Study 349, the results of this study could only be considered as supporting evidence and but could not be considered as a replication of those shown in Study 349.

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

From the reviewer's sensitivity analysis of prevention of developing NSAID-induced duodenal ulcer, it was found that a change in the ulceration status of just 1 Arthrotec patient from non-ulcerated to ulcerated, when there was no change or a change of 1 diclofenac patients from ulcerated to non-ulcerated would cause a shift in the 2-sided p-value from 0.028 to a p-value of greater than 0.05.

The results of this study were on borderline and not robust as seen in reviewer's sensitivity analysis. Hence, the study 013 failed to providing supporting evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg SR BID for prevention of developing NSAID-induced duodenal ulcer.

D. Comments to be conveyed to the Sponsor

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

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/S/

Milton C. Fan, Ph.D.  
Mathematical Statistician

This review consists of 13 pages of text and 2 pages of tables.

Concur: Dr. Huque  
Dr. Smith

/S/ 12/87  
2/14/87

cc:

- Archival NDA 20-607
- HFD-180
- HFD-180/Dr. Fredd
- HFD-180/Dr. Robie-Suh
- HFD-180/Mr. Strongin
- HFD-344/Dr. Lisook
- HFD-720
- HFD-720/Chron.
- HFD-720/Dr. Smith
- HFD-720/Dr. Huque
- HFD-720/Dr. Fan
- Dr. Fan/x73088/mcf/02/06/97

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Table 1 Comparability of Treatment Groups at Baseline --- Protocol 013

Intent-to-Treat Population				
Variable	Level	Arthrotec 75 mg BID (n=253)	Diclofenac 75 mg SR BID (n=261)	between treatment p-value
Sex	Male	79 (31%)	82 (31%)	0.963
	Female	174 (69%)	179 (69%)	
Age (mean)		59.2	59.5	
Height (cm) (mean)				
Weight (kg) (mean)				
History of Gastroduodenal or Upper GI Haemorrhage	Gastric ulcer	22 ( 9%)	16 ( 6%)	0.266
	Duodenal ulcer	7 ( 3%)	6 ( 2%)	0.736
	Upper GI Haemorrhage	7 ( 3%)	5 ( 2%)	0.523
History of Arthritic	Osteoarthritis	107 (42%)	106 (41%)	0.699
	Rheumatoid Arthritis	146 (58%)	155 (59%)	
Duration of Disease (yrs)		9.2	7.9	
Physician's Global Assessment	Very Good	5 ( 2%)	13 ( 5%)	0.238
	Good	80 (32%)	76 (29%)	
	Fair	128 (51%)	135 (52%)	
	Poor	36 (14%)	36 (14%)	
	Very Poor	4 ( 2%)	1 ( 1%)	
Patient's Global Assessment	Very Good	9 ( 4%)	13 ( 5%)	0.724
	Good	66 (26%)	71 (27%)	
	Fair	123 (49%)	121 (46%)	
	Poor	45 (18%)	50 (19%)	
	Very Poor	10 ( 4%)	6 ( 2%)	

P-values for other variables were obtained by this reviewer using Pearson's Chi-square test.

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Table 2 Sensitivity Analysis for Duodenal Ulcer for Study 013

Case 1: Diclofenac ulceration rate fixed at the observed rate of 5.4%  
(14 patients ulcerated over the total 261 patients).

Number of Arthrotec Patients: 253  
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
5	14	2.0%	5.4%	-3.4%	0.059

Observed number of patients ulcerated for this trial.  
Observed ulceration rates for this trial.

Case 2: Arthrotec ulceration rate fixed at the observed rate of 1.6%  
(4 patients ulcerated over the total 253 patients).

Number of Arthrotec Patients: 253  
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
4	13	1.6%	5.0%	-3.4%	0.046
4	12	1.6%	4.6%	-3.0%	0.073

Observed number of patients ulcerated for this trial.  
Observed ulceration rates for this trial.

Case 3: Arthrotec ulceration rate varied; Diclofenac ulceration rate varied.

Number of Arthrotec Patients: 253  
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
4	13	1.6%	5.0%	-3.4%	0.046
4	12	1.6%	4.6%	-3.0%	0.073
5	14	2.0%	5.4%	-3.4%	0.059
5	13	2.0%	5.0%	-3.0%	0.091

Observed number of patients ulcerated for this trial.  
Observed ulceration rates for this trial.

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MEMORANDUM OF STATISTICAL CONSULTATION -- NDA



Date: FEB 18 1997

NDA #: 20-607

Application: G.D. Searle & Co.

Name of Drug: Arthrotec (Diclofenac sodium/misoprostol)  
50 mg/200 mcg / 75 mg/200 mcg Tablets

Indication: Treatment of sign and symptoms of osteoarthritis  
and rheumatoid arthritis

Documents Reviewed: General Correspondence Dated December 23,  
1996  
NDA Suppl. Vol. 1-2 Dated December 20, 1995

Medical Reviewer: This consultation has been discussed with the  
medical officer, Kathy Robie-Suh, M.D., Ph.D.  
(HFD-180).

Key Words: Test of equivalence, pooling studies

Per Dr. Kathy Robie-Suh request, this reviewer has reviewed the  
sponsor's correspondence regarding comparing efficacy of  
misoprostol 100 mcg QID versus misoprostol 200 mcg BID.

A. Background

The sponsor was asked to provide information to determine whether  
changes in the misoprostol daily dose interval (e.g. BID versus  
QID) for the same total daily dose affects the efficacy and  
safety of that component of Arthrotec. The sponsor has provided  
response in the correspondence.

B. Sponsor's Analysis

The efficacy of misoprostol 100 mcg QID has not been compared  
directly with those of misoprostol 200 mcg BID. However, each  
dosing regimen has been evaluated in separate studies.

Misoprostol 100 mcg QID was evaluated in Studies U81-86-02-002  
and U81-86-02-003 (002/003). Both studies had identical designs  
and included patients with osteoarthritis treated with NSAIDs who

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continued these medications for the duration of the trials. A total of 421 patients were enrolled in the two studies combined, 143 were randomized to misoprostol 100 mcg QID, 140 to misoprostol 200 mcg QID and 138 to placebo. Patients underwent upper gastrointestinal (UGI) endoscopies at baseline and weeks 4, 8, and 12.

Misoprostol 200 mcg BID was evaluated in two studies of 12 weeks duration, Study S81-89-02-053 (053) and Study NN2-94-02-352 (352). Study 352 did not include UGI endoscopies. Study 053 included 1,618 patients with various underlying arthritides, receiving a variety of NSAIDs, who were randomized to misoprostol or placebo for 12 weeks. A total of 462 patients were randomized to misoprostol 200 mcg BID, 474 to 200 mcg TID, 228 to 200 mcg QID, and 454 to placebo. Patients underwent UGI endoscopies at baseline, weeks 4, 8, and 12.

The incidences of gastric ulcers (GU) in the misoprostol 100 mcg QID and misoprostol 200 mcg BID groups are given below.

#### Incidence of NSAID-Induced Gastric Ulcers

	Study 002/003		Study 053	
	Misoprostol 100 mcg QID (N=193)	Placebo (N=196)	Misoprostol 200 mcg BID (N=462)	Placebo (N=454)
GU Incidence	7 (3.6%)	28 (14.3%)	29 (6.3%)	51 (11.2%)
P-value	<0.05		<0.001	

Copied from page 10 of Response to FDA letter of 22 November 1996.

Both regimens were associated with significantly lower incidences of GU compared to placebo. In a logistic regression dose response analysis, submitted to FDA an addendum to misoprostol NDA, S-019 on December 20, 1995, the incidence of GU for the 200 mcg BID regimen fell within the 95% confidence interval of that for 100 mcg QID (Figure 1). Therefore, (according to the sponsor) the efficacy of the two misoprostol regimens for GU prevention are not different.

#### C. Reviewer's Comments and Evaluation

Studies 002 and 003 were pivotal studies submitted in the original NDA submission and compared efficacy of misoprostol 200 mcg QID and 100 mcg QID versus placebo in preventing NSAID-induced gastrointestinal damage. Both misoprostol QID doses were shown to be effective in preventing NSAID-induced gastric ulcers in Study 002, but in Study 003 only misoprostol 200 mcg QID was shown to be effective (see below).

#### Incidence of Gastric Ulcers

Study	Regimen	Rate
002	Miso 200 mcg QID	1/76 (1.4%)*
	Miso 100 mcg QID	5/77 (6.5%)*
	Placebo	19/76 (25%)
003	Miso 200 mcg QID	2/65 (3.1%)*
	Miso 100 mcg QID	5/66 (7.6%)
	Placebo	11/62 (17.7%)

\*Statistically significantly better than placebo at the 5% level.  
Compiled from Table 5, page 4 from Study Report 002 and 003, respectively.

In this correspondence the sponsor presents combined results of these two studies and indicates that in the pooled results misoprostol 100 mcg QID is effective in preventing NSAID-induced gastric ulcers.

It is unclear to this reviewer why the number of patients and incidence of gastric ulcers in the combined results presented in the sponsor's correspondence and report (N81-95-07-825) are different from those obtained from the individual study reports for Study 002 and Study 003. The incidence rate of gastric ulcers was much lower than those from the individual study (3.6% versus 6.5% and 7.6%, respectively for Studies 002 and 003). The sponsor's combined results are biased in favor of misoprostol 100 mcg QID.

The sponsor's approach to show that the efficacy of the two misoprostol regimens for GU prevention are not different is

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