The following table indicates the studies that were reviewed (indicated by double asterisk) and those which were not reviewed.

Study No	Title and Comment
NN2-91-02-332	Open-label, crossover study to assess the single-dose bioavailability of diclofenac and misoprostol from diclofenac/misoprostol combination tablets given to healthy male subjects under fasting conditions** (page 15)
EB2-87-02-270	A comparison of pharmacokinetic profiles of misoprostol and diclofenac from single doses of misoprostol and diclofenac, alone, coadministered as separate formulations and as a combination tablet. Comment: The design of this study was similar as that of NN2-92-06-332 except that each treatment was given after a meal. Twelve subject were included in the study. Since the results of Study NN2-92-06-332, which is pivotal, were included in the proposed labeling, and the results of this study were not included in the labeling, this study was not reviewed.
EN2-88-02-293	Effect of coadministration on the absorption of misoprostol and diclofenac sodium Comment: The design of this study was similar as that of NN2-92-06-332 except that each treatment was given after a meal. Thirty-seven healthy subjects were included in the study. Since the results of Study NN2-92-06-332, which is pivotal, were included in the proposed labeling, and the results of this study were not included in the labeling, this study was not reviewed.
NN2-93-02-346	An open label study to assess the single-dose oral bioavailability of diclofenac/misoprostol combination tablets in healthy subjects** (page 20)
NN2-89-02-316	Comparative bioavailability of three formulations of diclofenac tablets: the Geigy Pharmaceuticals U.S. formulation, the Geigy Pharmaceuticals Canada formulation, and the Searle formulation with placebo
NN2-89-02-303	Comparative bioavailability of three formulations of diclofenac tablets; the Geigy Pharmaceuticals U.S. formulation, the Geigy Pharmaceuticals Canada formulation, and the Searle formulation with placebo outer shell Comment: In this study all doses of diclofenac were taken with food. Comparative bioavailability Study NN2-90-06-316 was repeated, where all doses were given under fasting conditions.

EN2-89-02-302	Open label, randomized, 3-way crossover study to compare the pharmacokinetics of diclofenac given to healthy male volunteers as the Geigy Pharmaceuticals European formulation, the Geigy Pharmaceuticals U.S.A. formulation, or as a combination tablet with placebo outer shell
NN2-91-02-342	Open-label, crossover study in healthy male subjects to compare the bioavailability of diclofenac from diclofenac sodium tablets manufactured by Searle and Ciba-Geigy** (page 28)
NN2-90-02-329	Comparative bioavailability of diclofenac from diclofenac sodium tablets manufactured by Searle and Ciba-Geigy Comment: Since the same lots of tablets used in this study were retested to compare the bioavailability of diclofenac in Study NN2-92-06-342, this study was not reviewed.
NN2-91-02-343 PIVOTAL BE	An open-label, crossover study to assess the bioavailability of diclofenac and misoprostol from two formulations of diclofenac/misoprostol combination tablets** (page 31)
NN2-93-02-345	Open label, randomized, crossover study to compare the bioavailability of diclofenac and misoprostol acid from two formulations of diclofenac sodium/misoprostol combination tablets given to healthy subjects under fasted conditions** (page 35)
NN2-95-02-354 PIVOTAL BE	Amended integrated clinical and statistical report for an open label, randomized crossover study in healthy adult subjects to compare the bioequivalence of Arthrotec tablets containing Diclofenac relative to reference Arthrotec tablets** (page 39)
NN2-94-02-353 PIVOTAL BE	An open label, randomized, crossover study in healthy adult subjects to compare the bioavailability of diclofenac and misoprostol acid from diclofenac/misoprostol combination tablets manufactured at two different locations** (page 45)
NB2-89-02-299	Effect of misoprostol on the single-dose and multiple-dose pharmacokinetics of diclofenac in elderly subjects** (page 50)
NN2-91-02-338	On open-label study to assess the steady-state bioavailability profile of diclofenac/misoprostol combination tablets in healthy male subjects** (page 54)

NN2-93-02-347 An open label, randomized, crossover study to assess the multiple-dose bioavailability profile of diclofenac/misoprostol combination tablets given to healthy subjects under fed and fasted conditions** (page 57)

NN2-94-02-350 An open label, randomized, crossover study to compare the bioavailability of diclofenac from multiple doses of diclofenac/misoprostol combination tablets given b.i.d. and t.i.d. to healthy subjects** (page 62)

BIOEQUIVALENCE OF ARTHROTEC 50 VS. INDIVIDUAL COMPONENTS AS MARKETED TABLETS

Study No.: NN2-91-02-332 **Volume:** 1.32 **Page:** 6-2180

Title: Open-label, crossover study to assess the single-dose bioavailability of diclofenac and misoprostol from diclofenac/misoprostol combination tablets given to healthy male subjects under fasting conditions

Clinical Investigator

Dates of Study: 05/11/1991 - 06/28/1991

Objective: To assess the bioavailability of diclofenac and misoprostol from diclofenac/misoprostol combination tablets given to healthy male subjects under fasting conditions; marketed diclofenac sodium and misoprostol tablets given as separate formulations were used as reference products.

Study Design: Open-label, randomized, single-dose, four-treatment crossover study with four periods and 12 different sequences of treatment administration. A total of 37 healthy male subjects, 18-42 years of age, were enrolled in the study; subject 1 withdrew after one treatment and was replaced by subject 901; 36 subjects completed following all four treatments:

- One misoprostol 200 mcg tablet (Cytotec, marketed in U.S. by Searle), lot no. 1290-243
- One enteric-coated diclofenac sodium 50 mg tablet (Voltaren, marketed in U.S. by Geigy Pharmaceuticals), lot no. 1T129614.
- One misoprostol 200 mcg tablet plus one enteric-coated diclofenac sodium 50 mg tablet coadministered.
- One diclofenac sodium 50 mg/misoprostol 200 mcg combination tablet enteric coating formulation, , lot no. F9101/033,

Each treatment was administered after an overnight fast, followed by an additional four-hour fast; subjects crossed-over to the next treatment after a 7-day washout. Blood samples for determination of diclofenac and/or misoprostol acid plasma concentrations were obtained prior to dose and at the following times: for diclofenac, at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6 and 8 hours after dose; for misoprostol acid, at 5, 10, 15, 20, 30, and 45 minutes and 1, 2, and 4 hours after dose.

Assay Method:

Diclofenac:

Misoprostol:

Data Analysis: The maximum observed plasma concentration (Cmax), time to Cmax (tmax), and area under the curve (AUC) for diclofenac and/or misoprostol acid were determined for each treatment. For diclofenac, AUC(0-∞) from 0 to infinity was calculated. For misoprostol acid, the firm has reported that AUC(0-∞) was not determined due to the poor fit of the linear regression lines, resulting in unreliable values of elimination half-life. AUC(0-lqc) for misoprostol acid was determined. The least squares means were obtained by the analysis of variance with sequence, subject within sequence, period, and treatment as factors. AUC and Cmax were logarithmically transformed prior to analysis, so the least square means presented for these variables are geometric means.

Mean ratios with 90% confidence intervals were used to assess the relative bioavailability of each of the following pairs of treatments: combination tablet vs. diclofenac or misoprostol tablet alone; combination tablet vs. coadministration of diclofenac and misoprostol; coadministration of diclofenac and misoprostol vs. diclofenac or misoprostol tablet alone. All statistical testing was done at the two-sided 5% level of significance.

Results: The firm provided the following:

Mean (%CV) pharmacokinetic parameters of diclofenac after following treatments are:

Treatment (N=36)	Cmax (ng/mL)	tmax (hr)	AUC(0-∞) (hr.ng/mL)
Voltaren	1299 (34)	2.4 (41)	1209 (24)
Voltaren + Cytotec	1336 (29)	1.9 (50)	1104 (22)
Arthrotec 50	1207 (30)	2.4 (41)	1244 (20)

For subject #32, since all diclofenac concentration values were below assay sensitivity following the coadministration treatment, thirty-five values out of 36 for diclofenac Cmax, AUC and tmax were included in the summary statistics for the coadministration treatment.

The geometric mean ratio and 90% confidence interval (C.I.) for diclofenac for each pair of treatments are:

Treatment Comparison	Parameter	Ratio	90% C.I.
Arthrotec 50/ Voltaren	AUC(0-∞)	103.8%	(97.7%, 110.3%)
	Cmax	94.2%	(84.3 %, 105.3%)
Arthrotec 50/ Voltaren + Cytotec	AUC(0-∞)	112.7%	(106.0%, 119.9%)
	Cmax	88.7%	(79.3%, 99.2%)
Voltaren + Cytotec/ Voltaren	AUC(0-∞)	92.1%	(86.6%, 97.9%)
	Cmax	106.2%	(94.9%, 118.8%)

Mean (%CV) pharmacokinetic parameters of misoprostol acid after following treatments are:

Treatment (N=36)	Cmax (pg/mL)	tmax (hr)	AUC(0-lqc) (hr.pg/mL)
Cytotec	478 (42)	0.3 (42)	256 (49)
Cytotec + Voltaren	476 (43)	0.3 (32)	244 (41)
Arthrotec 50	441 (31)	0.3 (43)	235 (41)

For subject #34, since all misoprostol acid concentration values were also below assay sensitivity following the coadministration treatment, thirty-five values out of 36 for misoprostol acid Cmax, AUC(0-lqc) and tmax were included in the summary statistics for the coadministration treatment.

The geometric mean ratio and 90% confidence interval (C.I.) for misoprostol acid for each pair of treatments are:

Treatment Comparison	Parameter	Ratio	90% C.I.
Arthrotec 50/ Cytotec	AUC(0-lqc)	93.9%	(82.6%, 106.8%)
	Cmax	96.4%	(85.3%, 109.0%)
Arthrotec 50/ Cytotec + Voltaren	AUC(0-lqc)	95.8%	(84.1%, 109.1%))
	Cmax	97.2%	(85.9%, 110.0%)
Cytotec + Voltaren/ Cytotec	AUC(0-lqc)	98.0%	(86.0%, 111.6%)
	Cmax	99.2%	(87.7%, 112.3%)

Comments:

1. There is a discrepancy between AUC values for diclofenac determined by this reviewer and those reported from the sponsor. Following administration of Voltaren alone, mean AUC(0-∞) reported from the sponsor was 1209.44 hr.ng/ml, whereas that obtained by this reviewer was 1373.23 hr.ng/ml. Following coadministration of Voltaren and Cytotec, mean AUC(0-∞) from the sponsor and this reviewer were 1103.98 and 1399.84 hr.ng/ml, respectively. Following Arthrotec 50, those were 1244.06 and 1396.19 hr.ng/ml, respectively. However, this reviewer obtained similar 90% C.I.s as sponsor's.

2. There is a discrepancy between AUC(0-lqc) values for misoprostol acid determined by this reviewer and those reported from the sponsor. Following Cytotec alone, Cytotec + Voltaren, and Arthrotec 50, those obtained by this reviewer were 285, 260 and 257 pg.hr/ml, respectively. Those reported from the sponsor were 256, 244 and 235 pg.hr/ml, respectively.

3. The firm reported that AUC(0-∞) for misoprostol acid was not determined because of the poor fit of the linear regression lines, resulting in unreliable values of elimination half-life. Because of the short half-life (about 30 minutes) of misoprostol acid, the firm said that it is expected that AUC(0-lqc) contributed more than 80% of AUC(0-∞). This reviewer obtained AUC(0-∞) for misoprostol acid. Twenty-six, twenty-nine, and thirty-one subjects were included in the calculations of AUC(0-∞) after administration of Cytotec alone, Cytotec + Voltaren, and Arthrotec 50, respectively. All the 90% C.I.s obtained for misoprostol acid AUC(0-∞) passed the bioequivalence criteria.

4. Following treatment with the combination tablet, the range in the periods of lag time (t_{lag}) was (median 1.5 hours) and comparable to the t_{lag} values following administration of the diclofenac tablet alone (range , median 1.5 hours). The range in t_{lag} values was wider following diclofenac coadministered with misoprostol (range hours, median 1.25 hours). Absorption of diclofenac was rapid after the lag period and, in most subjects, Cmax occurred within 1 hour following appearance of drug in plasma.

5. The AUC(0-lqc) for diclofenac contributed about 99% of AUC(0-∞). Blood samples for diclofenac were collected for 8 hours postdose.

6. It should be noted that Arthrotec 50 used in this study is the organic-based enteric coating formulation.

7. The misoprostol acid levels observed in this study are quite different from those in other studies.

Conclusions: Based on the analyses results from sponsor and this reviewer, it is concluded that

- Arthrotec 50 is bioequivalent to coadministration of Voltaren and Cytotec for diclofenac AUC and misoprostol acid AUC and Cmax. However, the diclofenac Cmax 90% CI (79.3%, 99.2%) narrowly missed the standard confidence interval criteria (80%, 125%) for bioequivalence.

- Arthrotec 50 is bioequivalent to Voltaren alone for diclofenac AUC and Cmax; Arthrotec 50 mg is also bioequivalent to Cytotec alone for misoprostol acid AUC and Cmax.

- Voltaren coadministered with Cytotec was bioequivalent to Voltaren alone for diclofenac AUC and Cmax.

- Cytotec coadministered with Voltaren was bioequivalent to Cytotec alone for misoprostol acid AUC and Cmax.

Sponsor's Labeling Claim: The pharmacokinetics of the fixed combination of diclofenac sodium and misoprostol are not different from the pharmacokinetics of the two individual components, and there are no pharmacokinetic interactions between two components. Following oral administration of a single dose of ARTHROTEC® 50 (50 mg diclofenac sodium core) to healthy subjects under fasted conditions, the mean (SD) Cmax, AUC and Tmax for diclofenac were 1.21 (0.36) mcg/mL, 1.24 (0.24) h.mcg/mL and 2.4 (1.0) h, respectively, while the Cmax, AUC and Tmax for misoprostol were 441 (137) pg/mL, 235 (96) h.pg/mL and 0.30 (0.13) h, respectively.

Labeling Comment: The first sentence is OK. However, the firm is recommended to replace the pharmacokinetic parameters for diclofenac and misoprostol acid from ARTHROTEC 50 with more suitable values.

BIOEQUIVALENCE OF ARTHROTEC 75 VS. INDIVIDUAL COMPONENTS AS MARKETED TABLETS

Study No.: NN2-93-02-346 **Volume:** 1.36 **Page:** 6-3822

Title: An Open Label Study to Assess the Single-Dose Oral Bioavailability of Diclofenac/Misoprostol Combination Tablets in Healthy Subjects.

Dates of Study: 01/10/94 - 03/09/94

Objective: To assess the bioavailability of diclofenac and misoprostol from diclofenac/misoprostol combination tablets given to healthy male subjects under fasting conditions; marketed diclofenac sodium and misoprostol tablets given as separate formulations were used as reference products.

Formulations:

- Misoprostol 200 mcg tablet (Cytotec), commercial lot no. 3H391, packaging lot no. RCT 9515.
- Enteric-coated diclofenac sodium 75 mg tablet (Voltaren), commercial lot no. 2JT5120, packaging lot no. RCT 9514.
- Diclofenac sodium 75 mg/misoprostol 200 mcg combination tablet, packaging lot no. RCT 9511

Study Design: Single-center, open-label, crossover study with four-treatments:

- misoprostol 200 mcg alone;
- diclofenac 75 mg alone;
- diclofenac 75 mg + misoprostol 200 mcg coadministration;
- diclofenac 75 mg/misoprostol 200 mcg combination tablet.

Forty-one healthy volunteers (33 males, 8 females), ; were enrolled in the study: five subjects withdrew prior to study completion; 36 subjects completed the study. Subjects were randomized to one of eight sequences of treatment administration and received a single dose of each treatment under fasted conditions on days 1, 8, 15 and 22.

Blood samples for determination of diclofenac were collected prior to and at predetermined intervals up to 12 hour postdose. Blood samples for determination of misoprostol acid were collected prior to and at predetermined intervals up to 4 hours postdose.

Data Analysis: Noncompartmental pharmacokinetic parameters were determined as follows: area under the concentration-time curve (AUC); maximum observed plasma concentration (Cmax); time to Cmax (tmax). The firm reported that AUC(0-∞) for diclofenac was not calculated because for some subjects, an exponential elimination model did not fit the observed data from the terminal portion of the plasma concentration-time curve. For misoprostol acid, both AUC(0-lqc) and AUC(0-∞) were calculated. The ratio and corresponding 90% confidence interval (CI) for each parameter were used to assess the relative bioavailability of the following treatments: combination tablet vs. diclofenac or misoprostol alone; diclofenac+misoprostol coadministration vs. diclofenac or misoprostol alone; combination tablet vs. diclofenac+misoprostol coadministration. The ANOVA model contained terms for treatment sequence, subject (nested within sequence), period, first order carryover and treatment.

Assay Method:

Diclofenac:

Misoprostol:

Results: The firm provided the following:

Mean (%CV) pharmacokinetic parameters of diclofenac after following treatments are:

Treatment (N=36)	Cmax (ng/mL)	tmax (hr)	AUC(0-12) (hr.ng/mL)
Voltaren	2367 (56)	1.9 (36)	2609 (45)
Voltaren + Cytotec	2064 (63)	2.2 (55)	2496 (53)
Arthrotec 75	2025 (99)	2.0 (69)	2773 (49)

The geometric mean ratio and 90% confidence interval (C.I.) for diclofenac for each pair of treatments are:

Treatment Comparison	Parameter (N=35)	Ratio	90% C.I.	F-test p-value
Arthrotec 75/ Voltaren	AUC(0-lqc)	101.8%	(87.8%, 118.0%)	0.843
	Cmax	73.4%	(58.5 %, 92.1%)	0.026
Arthrotec 75/ Voltaren + Cytotec	AUC(0-lqc)	108.6%	(93.6%, 125.9%)	0.356
	Cmax	75.9%	(60.5%, 95.2%)	0.046
Voltaren + Cytotec/ Voltaren	AUC(0-lqc)	93.7%	(80.8%, 108.7%)	0.468
	Cmax	96.7%	(77.1%, 121.3%)	0.806

Mean (%CV) pharmacokinetic parameters of misoprostol acid after following treatments are:

Treatment (N=36)	Cmax (pg/mL)	tmax (hr)	AUC(0-4) (hr.pg/mL)
Cytotec	290 (45)	0.35 (34)	176 (33)
Cytotec + Voltaren	288 (48)	0.40 (156)	158 (45)
Arthrotec 75	304 (36)	0.26 (35)	177 (27)

The geometric mean ratio and 90% confidence interval (C.I.) for misoprostol acid for each pair of treatments are:

Treatment Comparison	Parameter	Ratio	90% C.I.	F-test p-value
Arthrotec 75/ Cytotec	AUC(0-∞)	97.8%	(88.0%, 108.7%)	0.731
	AUC(0-lqc)	102.7%	(86.0%, 122.6%)	0.805
	Cmax	106.8%	(90.0%, 126.8%)	0.523
Arthrotec 75mg/ Cytotec + Voltaren	AUC(0-∞)	112.8%	(101.5%, 125.4%)	0.061
	AUC(0-lqc)	125.9%	(105.4%, 150.4%)	0.034
	Cmax	113.4%	(95.5%, 134.6%)	0.226
Cytotec + Voltaren/ Cytotec	AUC(0-∞)	86.7%	(78.0%, 96.4%)	0.028
	AUC(0-lqc)	81.5%	(68.3%, 97.4%)	0.060
	Cmax	94.2%	(79.4%, 111.8%)	0.564

Comments:

- This reviewer calculated AUC(0-∞) for diclofenac. It was found that AUC(0-lqc) contributed more than 95% of AUC(0-∞). The ANOVA model used by this reviewer contained sequence, subject within sequence, period, and treatment as factors, whereas the model used by the sponsor included terms for sequence, subject nested within sequence, period, first order carryover and treatment as factors. The carryover effect was not found to be statistically significant. The 90% C.I. and results of two one-sided tests procedure obtained by this reviewer were similar to those of sponsor's.

Conclusions: Based on the analyses results from sponsor and this reviewer, it is concluded:

- The extent of diclofenac and misoprostol acid absorption (AUC) from Arthrotec 75 was equivalent to that from marketed Voltaren or Cytotec alone. However, mean diclofenac Cmax for Arthrotec 75 was significantly lower ($p=0.026$) than that for Voltaren alone; bioequivalency of the two treatments could not be demonstrated (Cmax ratio = 73.4%, 90% CI = 58.5%, 92.1%). Mean misoprostol acid Cmax for Arthrotec 75 was not significantly different from that for misoprostol alone ($p=0.523$); however, the treatments did not meet the bioequivalence criteria for the rate of absorption (Cmax ratio = 106.8%, 90% CI = 90.0%, 126.8%); marginally failed in upper bound.

- Arthrotec 75 tablet was not bioequivalent to marketed Voltaren 75 mg tablet and marketed Cytotec 200 mcg tablet given concomitantly with respect to both diclofenac and misoprostol acid AUC and Cmax.

- Diclofenac coadministered with misoprostol was equivalent to diclofenac tablets given alone for AUC, but not for Cmax; the lower limit of the 90% C.I. was slightly below 80%. Misoprostol coadministered with diclofenac was not equivalent to the misoprostol tablet alone for misoprostol acid AUC or Cmax.

Sponsor's Labeling Claim: Diclofenac sodium Cmax, AUC and Tmax following a single oral dose of ARTHROTEC® 75 (75 mg diclofenac sodium core) were 2.03 (2.00) mcg/mL, 2.77 (1.35) h.mcg/mL and 2.0(1.4) h, respectively; misoprostol acid plasma concentrations were also similar to those obtained with ARTHROTEC® 50. The rate and extent of diclofenac sodium and misoprostol acid absorption from ARTHROTEC® 50 and ARTHROTEC® 75 were equivalent to those from commercially available diclofenac sodium and misoprostol each administered alone. There are no pharmcokinetic interactions between diclofenac sodium and misoprostol when single doses of ARTHROTEC® 50 or ARTHROTEC® 75 are administered to normal subjects.

Labeling Comment: The firm's proposed labeling should be replaced by following:

"Diclofenac sodium Cmax, AUC and Tmax following a single oral dose of ARTHROTEC® 75 (75 mg diclofenac sodium core) were 2.03 (2.00) mcg/mL, 2.77 (1.35) h.mcg/mL and 2.0(1.4) h, respectively; misoprostol acid plasma concentrations were also similar to those obtained with ARTHROTEC® 50. The extent of diclofenac sodium and misoprostol acid absorption from ARTHROTEC® 75 was equivalent to that from commercially available diclofenac sodium and misoprostol each administered alone. However, mean diclofenac Cmax for ARTHROTEC® 75 was significantly lower than that for diclofenac alone. Misoprostol acid Cmax for ARTHROTEC® 75 was not equivalent to that for misoprostol alone. ARTHROTEC® 75 cannot be considered bioequivalent to coadministration of marketed diclofenac sodium and misoprostol in terms of AUC and Cmax for either components."

BIOEQUIVALENCE OF DICLOFENAC/PLACEBO AND MARKETED VOLTAREN TABLETS

Study No.: NN2-89-02-316 **Volume:** 1.31 **Page:** 6-1744

Title: Comparative Bioavailability of Three Formulations of Diclofenac Tablets: the Geigy Pharmaceuticals U.S. Formulation, the Geigy Pharmaceuticals Canada Formulation, and the Searle Formulation with Placebo Outer Shell

Objectives: The primary objective is to compare the bioavailability of diclofenac from three formulations of 50 mg enteric-coated diclofenac sodium tablets, namely the Geigy Pharmaceuticals U.S. formulation, the Geigy Pharmaceuticals Canada formulation, and the Searle formulation. A secondary objective was to compare the bioavailability of diclofenac from two different lots of the Geigy Pharmaceuticals Canada formulation.

Study Design: Open-label, randomized, balanced, single-dose crossover study with four treatments: a) one Voltaren tablet containing 50 mg of diclofenac sodium (Geigy U.S., lot no. 1T117130; one Voltaren tablet containing 50 mg of diclofenac sodium (Geigy Canada, lot no. 908300 , c) one Voltaren tablet containing 50 mg of diclofenac sodium (Geigy Canada lot no. 915900 ; d) one diclofenac/placebo tablet (Searle, lot no. GSA49-224). All doses were given under fasting conditions. A seven day washout separated each dose.

Blood samples (10 ml each) were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 12 hours postdose.

The bioequivalance of each pair of diclofenac formulations (Searle and Geigy U.S., Searle and Geigy Canada Geigy U.S. and Geigy Canada Geigy Canada was determined.

Twenty-six healthy male subjects, aged , were enrolled in the study. Two subjects withdrew: 24 subjects completed the study.

Data Analysis: The PK parameters AUC(0-∞) and Cmax were log-transformed prior to analyses. The ANOVA model contained terms for treatment sequence, subject (nested within sequence), period, treatment, and carryover effects.

Assay Method: Diclofenac concentrations

Results: The firm provided the following:

The diclofenac mean (%CV) values for AUC(0-∞), Cmax and tmax in 24 healthy subjects under fasted conditions are:

Parameter	Diclofenac/Placebo	Voltaren (U.S.)
AUC(0-∞), hr.ng/ml	1299 (29)	1252 (30)
Cmax, ng/ml	1018 (30)	1138 (39)
tmax, hr	2.7 (27)	2.7 (28)

Analysis of variance showed no statistically significant treatment differences in mean AUC, Cmax, and tmax values when the Searle diclofenac/placebo tablets were compared to the marketed Voltaren (Geigy U.S.) tablets.

The geometric mean AUC and Cmax ratios and confidence intervals are:

Treatment Comparison	Parameter	Ratio	90% C.I.
Diclofenac/Placebo	AUC(0-∞)	103.3%	(96.5%, 110.5%)
Voltaren (U.S.)	Cmax	91.8%	(80.6%, 104.6%)

Comments:

- To assess the safety and efficacy of diclofenac with and without misoprostol, the diclofenac/placebo tablets which were identical in appearance to Arthrotec but did not contain misoprostol in outer mantle were formulated. The objective of this study was to assess whether the diclofenac/placebo tablets had acceptable bioavailability compared to enteric-coated diclofenac sodium 50 mg tablets currently marketed in the U.S. Geigy Pharmaceuticals (Voltaren).

- The ANOVA model used by the sponsor included terms for sequence, subject nested within sequence, period, first order carryover and treatment as factors. This reviewer reanalyzed the data using the ANOVA model which contained terms for treatment, period, sequence and subject (nested within the sequence) and obtained the similar results as sponsor's; the

diclofenac/placebo tablets were bioequivalent to the marketed Voltaren (U.S.) in terms of diclofenac AUC and Cmax.

Conclusions: Based on the analyses results of the sponsor and this reviewer, it is concluded:

- The Searle and Geigy U.S. formulations demonstrated equivalence in terms of AUC and Cmax.

BIOEQUIVALENCE OF DICLOFENAC/PLACEBO AND MARKETED VOLTAREN TABLETS

Study No.: NN2-91-02-342 **Volume:** 1.33 **Page:** 6-2682

Title: Open-label, crossover study in healthy male subjects to compare the bioavailability of diclofenac from diclofenac sodium tablets manufactured by Searle and Ciba-Geigy

Dates of Study: 10/19/91 - 11/02/91

Objectives: To compare the bioavailability of diclofenac from two formulations of Searle diclofenac/placebo tablets given to healthy male subjects under fasting conditions; and to compare the bioavailability of diclofenac from each formulation of Searle diclofenac/placebo tablets to enteric-coated diclofenac sodium tablets marketed in the U.S. by Geigy Pharmaceuticals.

Formulations:

- One tablet containing an enteric-coated core of diclofenac sodium 50 mg within a placebo mantle [Searle
- One tablet containing an enteric-coated core of diclofenac sodium 50 mg within a placebo mantle [Searle
- One enteric-coated diclofenac sodium 50 mg tablet (Voltaren, marketed in the U.S. by Geigy Pharmaceuticals [Geigy U.S.]).

Study Design: Open label, randomized, single dose, three-treatment crossover study with three periods and six different sequences of treatment administration. Each treatment was administered after an overnight fast, followed by an additional four-hour fast; subjects crossed-over to the next treatment after a 7-day washout.

24 healthy male subjects, years of age, enrolled in and completed the study.

Blood samples (10 ml) for determination of diclofenac plasma concentrations were obtained prior to dose (0 hr) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, and 12 hours after each dose.

Data Analysis: The maximum observed plasma concentration (Cmax), time to Cmax (tmax), and area under the curve from time 0 to infinity [AUC(0-∞)] were determined for each treatment. The PK parameters AUC(0-∞) and Cmax were log-transformed prior to analyses. Mean ratios with confidence intervals were used to assess the relative bioavailability of each of the following pairs of treatments : Searle s. Searle Searle- s. Geigy U.S.; Searle vs. Geigy U.S.

Overall, assay method and quality control data are acceptable.

Results: The firm provided the following:

Treatment (N=24)	Cmax (ng/ml)	tmax (hr)	AUC(0-∞) (hr.ng/ml)
Diclofenac/Placebo-A	1169 (30)	2.4 (41)	1426 (16)
Diclofenac/Placebo-B	1106 (33) 1149[b](26)	2.8 (74) 2.4[b](32)	1409 (20)
Voltaren (U.S.)	1227 (29)	2.6 (30)	1406 (17)

[b] Atypical Cmax and tmax values for subject #16. The onset of absorption following the Searle-B treatment was markedly delayed and only the 12 hour diclofenac concentration value was above assay sensitivity; AUC(0-∞) could not be calculated and bioequivalence analyses were performed with and without the diclofenac/placebo-B Cmax and tmax data for subject #16.

The geometric mean ratio with the associated 90% confidence interval for diclofenac AUC and Cmax for each pair of treatments are:

Treatment Pair	Parameter	Ratio	90% C.I.
Diclofenac/Placebo-B Diclofenac/Placebo-A	AUC(0-∞) Cmax	97.2% 96.2%	(91.4%, 103.3%) (85.3%, 108.4%)
Diclofenac/Placebo-B Voltaren (U.S.)	AUC(0-∞) Cmax	98.6% 91.2%	(92.7%, 104.8%) (80.9%, 102.8%)
Diclofenac/Placebo-A Voltaren (U.S.)	AUC(0-∞) Cmax	101.4% 94.8%	(95.5%, 107.7%) (84.2%, 106.6%)

Note that above table shows the data without subject #16.

Analysis of variance showed no statistically significant differences between treatments for AUC(0-∞), Cmax or tmax.

Comments: The primary objective of this study was to compare the bioavailability of diclofenac chemical in diclofenac/placebo tablets supplied to the diclofenac chemical in diclofenac/placebo tablets used in previous clinical trials (supplied by

Conclusions: This reviewer agrees with the firm's following conclusions:

- The two formulations of diclofenac/placebo were bioequivalent with respect to diclofenac AUC and Cmax.

- Both formulations of diclofenac/placebo tablets were bioequivalent to Voltaren (U.S.) tablets for AUC; bioequivalence for Cmax was demonstrated when an atypical diclofenac/placebo-B Cmax value (111.1 ng/ml at 12 hr postdose) for one outlier subject was excluded from the analyses.

BIOEQUIVALENCE OF ARTHROTEC 50 MG CLINICAL SUPPLIES (PIVOTAL BE)

Study No.: NN2-91-02-343 **Volume:** 1.34 **Page:** 6-2892

Title: An open-label, crossover study to assess the bioavailability of diclofenac and misoprostol from two formulations of diclofenac/misoprostol combination tablets

Dates of Study: 03/14/92 - 03/28/92

Objective: To compare the bioavailability of diclofenac and misoprostol from aqueous diclofenac/simplex misoprostol combination tablets relative to the reference formulation of organic diclofenac/duplex misoprostol combination tablets, which have been used in previous clinical trials.

Formulations:

- Test formulation: diclofenac sodium 50 mg/simplex misoprostol 200 mcg combination tablet , package lot no. RCT 9244.
- Reference formulation: 10 mm organic diclofenac sodium 50 mg/duplex misoprostol 200 mcg combination tablet
  package lot no. RCT 9243.

Study Design: Open label, randomized, three-period crossover study with two treatments given in four different sequences of treatment administration; subjects received a single dose of each treatment during periods 1 and 2 of the study, and a replicate dose of one of the treatments during period 3. Each treatment was administered after an overnight fast, followed by an additional 4-hour fast; subjects crossed-over to the next treatment after a 7-day washout.

Twenty-four healthy male subjects, enrolled in and completed the study.

Blood samples for determination of diclofenac and misoprostol acid plasma concentrations were obtained prior to dose and at predetermined intervals for up to eight hours after each treatment.

Data Analysis: The maximum observed plasma concentration (Cmax), time to Cmax (tmax), and are under the curve (AUC) for diclofenac and misoprostol acid were determined for each treatment. AUC and Cmax values were log-transformed prior to analyses. Mean ratios with confidence intervals were used to assess the bioequivalence of the aqueous/simplex vs. organic/duplex tablets. Additional analyses were done to assess the relative bioavailability of the replicate vs. initial doses of each treatment.

The ANOVA models contained terms for sequence, subject (nested within sequence), period and treatment. For the assessment of the bioavailability of the replicate dose relative to the initial dose, ANOVA models with factors for sequence, subject (nested within sequence) and initial vs. replicate treatment were used.

Assay Method:

Results: The sponsor provided the following:

The relative bioavailability of diclofenac from test and reference tablets in 24 healthy subjects is:

Parameter	Treatment Means Test	Reference	Ratio Test/Ref.	90% C.I. for Ratio
AUC(0-∞)[a] (hr.ng/ml)	1365.0	1409.1	96.9%	(91.2%, 102.9%)
Cmax[a] (ng/ml)	1004.2*	1146.4	87.6%	(80.1%, 95.8%)
tmax[b] (hr)	1.69	2.28	74.2%	

[a] geometric least squares means
[b] least squares means

* $p<0.05$, statistically significant

ANOVA showed a statistically significant difference in mean diclofenac Cmax values ($p=0.017$).

The relative bioavailability of misoprostol acid from test and reference tablets in 24 healthy subjects is:

Parameter	Treatment Means Test	Reference	Ratio Test/Ref.	90% C.I. for Ratio
AUC(0-∞)[a] (hr.pg/ml)	167.5	160.2	104.50%	(96.8%, 112.9%)
Cmax[a] (pg/ml)	286.2	276.1	103.7%	(93.1%, 115.4%)
tmax[b] (hr)	0.28	0.29	94.1%	

[a] geometric least squares means
[b] least squares means

Replicate vs Initial Doses of Aqueous/Simplex Tablets

The relative differences in diclofenac AUC and Cmax for the replicate dose of aqueous/simplex tablets were within 20% of the initial dose (AUC ratio = 101.2%, 90% C.I. = 93.7%, 109.2%; Cmax ratio = 97.4%, 90% C.I. = 81.4%, 116.7%).

The relative differences in misoprostol acid AUC and Cmax for the replicate dose of aqueous/simplex tablets were within 20% of the initial dose, however, the lower limit of the C.I. for misoprostol acid AUC and Cmax fell outside the acceptable 80% limit (90% C.I. = 73.5%, 97.4% for AUC; 71.4%, 111.3% for Cmax).

Replicate vs Initial Doses of Organic/Duplex Tablets

The relative differences in diclofenac AUC and Cmax for the replicate dose of organic/duplex tablets were within 20% of the initial dose (AUC ratio = 105.0%, 90% C.I. = 95.6%, 115.4%; Cmax ratio = 99.2%, 90% C.I. = 86.5%, 113.8%).

The relative differences in misoprostol acid AUC and Cmax for the replicate dose of aqueous/simplex tablets were within 20% of the initial dose, however, the lower limit of the C.I. for misoprostol acid AUC and Cmax fell outside the acceptable 80% limit (90% C.I. = 72.1%, 105.1% for AUC; 77.9%, 111.5% for Cmax).

Comments:

- During product development, a number of formulation changes have been made to the diclofenac and misoprostol components of Arthrotec 50 mg. The bioavailability studies were conducted to link the proposed marketed formulations of Arthrotec 50 mg to the tablets used in clinical trials. The objective of this study was to compare the bioavailability of diclofenac and misoprostol from misoprostol combination tablets relative to the reference formulation of organic diclofenac misoprostol combination tablets was the original formulation used in early clinical efficacy/safety trials. was used in two pivotal U.S. clinical efficacy trials (NN2-95-06-349, NN2-95-06-352).

Conclusions: Based on the analyses results from sponsor and this reviewer, it can be concluded:

- The diclofenac core of the test tablet of aqueous/simplex tablets was bioequivalent to the reference organic/duplex tablet core with respect to diclofenac AUC and Cmax.

- The rate and extent of misoprostol acid bioavailability from the misoprostol mantles of the aqueous/simplex and organic/duplex formulations were equivalent.

BIOEQUIVALENCE OF ARTHROTEC 50 CLINICAL SUPPLIES

Study No.: NN2-93-02-345 **Volume:** 1.35 **Page:** 6-3352

Title: Open Label, Randomized, Crossover Study to Compare the Bioavailability of Diclofenac and Misoprostol Acid from Two Formulations of Diclofenac Sodium/Misoprostol Combination Tablets Given to Healthy Subjects Under Fasted Conditions

Dates of Study: 6 November 1993 - 16 December 1993

Objectives: To determine the bioavailability of diclofenac and misoprostol acid from a test formulation of diclofenac/misoprostol combination tablet
relative to the reference diclofenac/misoprostol tablet

Formulations:

- Test (T): Diclofenac sodium 50 mg/misoprostol 200 mcg combination tablet , packaged lot RCT 9503.
- Reference (R): Diclofenac sodium 50 mg/misoprostol 200 mcg combination tablet packaged lot RCT 9502.

Study Design: Single center, open-label, randomized, three-period crossover, replicate-design study with two treatments [test (T) and reference (R)] administered in one of two sequences T, R and R, or R, T and T on days 1, 8 and 15, respectively.

Blood samples for diclofenac and misoprostol acid assay were collected at predetermined times for eight hours postdose.

Twenty-six healthy male subjects, (mean age 31 years), were enrolled in the study; two subjects withdrew prior to completion; 24 subjects completed the study and were evaluable for bioavailability analyses.

Data Analysis: Noncompartmental pharmacokinetic parameter estimates for diclofenac and misoprostol acid area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (Cmax), and time to Cmax (tmax) were determined for each treatment. Cmax and AUC values were log-transformed before analyses.

Cmax and AUC values were normalized to compensate for differences in misoprostol and diclofenac sodium content of each formulation. The ratio and corresponding 90% confidence interval (C.I.)

for each parameter were used to assess the bioequivalence of the test and reference formulations and to assess the relative bioavailability of initial and replicate doses each treatment.

The ANOVA models contained terms for sequence, subject (nested within sequence), period, first order carryover and treatment. For the assessment of the bioavailability of the replicate dose relative to the initial dose, ANOVA models with factors for sequence, and initial vs. replicate treatment were used.

Assay Method:

Results: The relative bioavailability of diclofenac from test and reference tablets (N=19) is:

Parameter	Treatment Means Test	Reference	Ratio Test/Ref.	90% C.I. for Ratio
AUC(0-lqc)[a] (hr.ng/ml)	1432.6	1447.9	98.9%	(91.2%, 107.4%)
Cmax[a] (ng/ml)	1052.8	1176.7	89.5%	(77.5%, 103.3%)
tmax[b] (hr)	1.17	2.08	56.3%	

[a] geometric least squares means
[b] least squares means

Subject # 104, 105, 109, 111 and 124 had insufficient diclofenac concentration data (i.e., values missing and/or less than assay sensitivity limit), these subjects were not included in the statistical assessments.

The relative bioavailability of misoprostol acid from test and reference tablets (N=23) is:

Parameter	Treatment Means Test	Reference	Ratio Test/Ref.	90% C.I. for Ratio	F-test p value
AUC(0-∞)[a] (hr.pg/ml)	178.3	203.0	87.8%	(83.0%, 93.0%)	
AUC(0-lqc)[a] (hr.pg/ml)	153.4	181.4	84.6%	(79.1%, 90.5%)	
Cmax[a] (pg/ml)	285.0	340.7	83.7%	(77.9%, 89.8%)	
tmax[b] (hr)	0.32	0.30	109.4%		

[a] geometric least squares means
[b] least squares means

Subject #101 had an large AUC(0-∞) value (4209.5 hr.pg/ml for the reference product treatment), this value appeared to be an outlier, this subject was omitted from analysis.

Comments:

- The objective of this study was to evaluate the bioequivalence of Arthrotec 50 tablets with diclofenac cores manufactured at different sites. The firm has stated that the results of this study would not be used to demonstrate the bioequivalence of the proposed U.S. product.

- For the assessment of bioequivalence, the sponsor used SAS PROC GLM which contained terms for sequence, subject (nested within sequence), period, first order carryover and treatment as factors and the results are shown above. Since this is a replicate design study, this reviewer reanalyzed the diclofenac data using SAS PROC MIXED (random subject effect, random subject*treatment interaction, all other effects in the model are assumed fixed) and obtained the 90% confidence intervals of (74.9%, 106.8%) for Cmax and (89.6%, 107.8%) for AUC(0-lqc), respectively. In the statistical analyses, subject # 104, 105, 109, 111 and 124 were not included since those subjects had insufficient diclofenac concentration data (i.e., values missing and/or less than assay sensitivity limit).

- The firm has reported that when parameters were normalized to compensate for the 5.7% difference in misoprostol content between formulations, the test and reference tablets were

considered bioequivalent for misoprostol acid AUC(0-∞), AUC(0-lqc) and Cmax. However, the conclusion based on parameters which were corrected for the difference in misoprostol content is not justified.

Conclusions: Based on the analyses results of the sponsor and this reviewer, it is concluded:

- The diclofenac tablet was bioequivalent to the reference tablet with respect to extent of diclofenac bioavailability [AUC(0-lqc)], but not for Cmax.

- The bioequivalence of the misoprostol of the test and reference tablets was demonstrated for extent of misoprostol acid bioavailability [AUC(0-∞)], but not for Cmax.

BIOEQUIVALENCE OF ARTHROTEC 50 CLINICAL SUPPLIES (PIVOTAL BE)

Study No: NN2-95-02-354 **Volume:** 1.39 **Page:** 6-5207

Title: Amended integrated clinical and statistical report for an open label, randomized crossover study in healthy adult subjects to compare the bioequivalence of Arthrotec tablets containing Diclofenac relative to reference Arthrotec tablets

Dates of Study: 02/24/95 - 03/15/95

Objective: To compare the bioequivalence of two proposed U.S. formulations of diclofenac/misoprostol tablets manufactured with diclofenac supplied and vs. the Arthrotec tablets

Formulations:

- Proposed diclofenac 50 mg misoprostol 200 mcg, manufactured at
- Proposed diclofenac 50 mg misoprostol 200 mcg, manufactured at
- Reference tablets currently marketed in diclofenac 50 mg misoprostol 200 mcg, manufactured at

Study Design: Single-center, open-label, randomized, three period crossover study. Thirty-three healthy subjects (7 female, 26 male) (mean age 28 years) were enrolled in the study; three subjects withdrew before completion of the study; 30 subjects completed the study. Each subject received single oral doses of the following three formulations: 1) proposed product 2) proposed product and 3) reference tablets currently marketed in . Subjects were randomized to six sequences and received drug in a fasted state on days 1, 6 and 11.

Blood samples for measurement of diclofenac and misoprostol acid plasma concentrations were obtained prior to each dose and at predetermined intervals for 12 hours postdose.

Assay Methods:

Data Analysis: Non-compartmental pharmacokinetic parameter estimates for diclofenac and misoprostol acid area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (C_{max}), and time to C_{max} (t_{max}) were determined for each treatment; the lag time (t_{lag}) before the onset of diclofenac absorption from the enteric-coated core was also determined for each formulation. Cmax and AUC values were log-transformed before analyses. The ratio and corresponding 90% confidence interval (C.I.) for each parameter were used to assess the bioequivalence of the test and reference formulations. Bioequivalence for AUC or C_{max} was concluded if the 90% C.I. for the ratio fell within the predetermined range of 80% to 125%.

The ANOVA models contained terms for treatment sequence, subject (nested within sequence), treatment and first order carryover.

Results: The firm provided the following:

APPEARS THIS WAY
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APPEARS THIS WAY
ON ORIGINAL

/S/ 10/31/96

Hae-Ryun Choi, Ph.D.

Division of Pharmaceutical Evaluation II

ClinPharm/Biopharm Briefing on 10/18/96 (Drs. Lesko, M.Chen, Malinowski, Fleischer, Hussain, Shiu, Bashaw, Robie-Suh, Huang, Kaus, and Choi)

RD initialed by Lydia Kaus, Ph.D. /S/ 10/31/96

FT initialed by Lydia Kaus, Ph.D. /S/ 10/31/96

cc: NDA 20-607, HFD-180, HFD-870 (M.Chen, Kaus, Choi), HFD-340 (Viswanathan), HFD-870 (Chron, Drug, Reviewer)

APPEARS THIS WAY
ON ORIGINAL

Mean (%CV) pharmacokinetic parameters of diclofenac after following treatments in 30 subjects are:

Treatment		AUC(0-lqc) (hr.ng/ml)	Cmax (ng/ml)	Tmax (hr)
Proposed supplied by	Product diclofenac	1153 (21)	796 (37)	1.7 (77)
Proposed supplied by	Product diclofenac	1179 (32)	898 (41)	1.9 (117)
supplied by	diclofenac	1093 (32)	980 (44)	3.1 (84)

The geometric mean ratio and 90% confidence interval (C.I.) for diclofenac for each pair of treatments are:

Treatment Pair	Parameter	Ratio	90% C.I.
Product	AUC(0-lqc)	114.6%	(101.1%, 129.9%)
	AUC(0-∞)*	97.7%	(88.2%, 108.4%)
	Cmax	97.5%	(79.0%, 120.3%)
Product	AUC(0-lqc)	113.6%	(100.2%, 128.7%)
	AUC(0-∞)*	102.0%	(92.1%, 112.9%)
	Cmax	100.3%	(81.3%, 123.8%)
Product	AUC(0-lqc)	99.1%	(87.5%, 112.4%)
Product	AUC(0-∞)*	104.3%	(94.1%, 115.7%)
	Cmax	102.9%	(83.4%, 127.0%)

* N=20 for AUC(0-∞)

APPEARS THIS WAY
ON ORIGINAL

Mean (%CV) pharmacokinetic parameters of misoprostol acid after following treatments in 30 subjects are:

Treatment		AUC(0-lqc) (hr.pg/ml)	Cmax (pg/ml)	Tmax (hr)
Proposed [redacted] supplied by [redacted]	Product diclofenac	134 (40)	234 (34)	0.31 (33)
Proposed [redacted] supplied by	Product diclofenac	130 (46)	221 (55)	0.33 (32)
supplied by	diclofenac	147 (51)	234 (41)	0.35 (48)

The geometric mean ratio and 90% confidence interval (C.I.) for misoprostol acid for each pair of treatments are:

Treatment Pair	Parameter	Ratio	90% C.I.
Product	AUC(0-lqc)	95.4%	(84.8%, 107.3%)
	AUC(0-∞)*	97.4%	(86.7%, 109.4%)
	Cmax	99.8%	(85.4%, 116.6%)
Product	AUC(0-lqc)	90.0%	(80.0%, 101.2%)
	AUC(0-∞)*	106.0%	(94.0%, 119.6%)
	Cmax	87.8%	(75.2%, 102.6%)
Product	AUC(0-lqc)	94.3%	(83.9%, 106.1%)
Produc	AUC(0-∞)*	108.9%	(96.7%, 122.6%)
	Cmax	88.0%	(75.3%, 102.8%)

* N=17 for AUC(0-∞)

Comments:

- During clinical development, various manufacturing changes have been made to the diclofenac and misoprostol components of Arthrotec 50 mg. The bioavailability studies were conducted

to link the proposed marketed formulations to the tablets used in clinical trials. In this study, the firm stated that the marketed Canada tablets were chosen as the reference product because they were nearly identical in formulation to clinical supply I. The differences being in the misoprostol dispersion (duplex vs. simplex) and site(s) of manufacture The bioequivalence of clinical supply I and U.S. trial supply was evaluated in Study NN2-93-06-343. Therefore, the reference marketed Canada tablets are indirectly linked via clinical supply I to the tablets used in two pivotal U.S. clinical efficacy trials.

- The firm provided AUC(0-∞) values for diclofenac from only 20 subjects. This reviewer recalculated AUC(0-∞) for diclofenac; for Canadian, proposed and proposed product formulations, 28, 30 and 29 subjects were included in the calculations of diclofenac AUC(0-∞). It was found that AUC(0-lqc) contributed more than 90% of AUC(0-∞). The statistical model used by this reviewer included sequence, treatment, period and subject (within sequence) as factors, whereas the ANOVA model used by sponsor included the terms for sequence, subject within sequence, treatment and first order carryover. The firm's data showed that 90% C.I. for diclofenac AUC(0-lqc) ratio between product marketed formulation) and Canadian formulation did not pass the bioequivalency criteria. However, 90% C.I. for diclofenac AUC(0-∞) obtained from 20 subjects, passed. Cmax with 90% C.I. = 79.0-120.3% marginally missed establishing bioequivalence. This reviewer obtained the following: the 90 % C.I. for AUC(0-∞) passed the bioequivalency criteria; Cmax with 90% C.I.=73.9-107.9% bioequivalency was not established. With respect to the 90% C.I. obtained by this reviewer for diclofenac AUC(0-∞) ratio between U.S. product B and Canada formulation or between product and product both passed the bioequivalency criteria.

Conclusions: Based on the analyses results from the sponsor and this reviewer, it is concluded:

product

Equivalence was shown for the extent of diclofenac absorption in terms of AUC(0-∞). However, the rate of absorption in terms of Cmax was not equivalent.

Misoprostol acid was shown to be bioequivalent both in terms of the extent of absorption [AUC(0-∞) and AUC(0-lqc)] and the rate of absorption (Cmax).

product

Diclofenac was shown to be bioequivalent both in terms of the extent of absorption [AUC(0-∞)] and the rate of absorption (Cmax).

Misoprostol acid equivalence was established in terms of AUC(0-∞), AUC(0-lqc), but not for Cmax.

product vs. product

Equivalence was shown for the extent of diclofenac absorption in terms of AUC(0-lqc) and AUC(0-∞). However, the rate of absorption in terms of Cmax was not equivalent.

Equivalence was shown for the extent of misoprostol acid absorption in terms of AUC(0-lqc) and AUC(0-∞), but not for Cmax.

BIOEQUIVALENCE OF ARTHROTEC 75 CLINICAL SUPPLIES (PIVOTAL BE)

Study No: NN2-94-02-353 **Volume:** 1.38 **Page:** 6-4846

Title: An open label, randomized, crossover study in healthy adult subjects to compare the bioavailability of diclofenac and misoprostol acid from diclofenac/misoprostol combination tablets manufactured at two different locations

Dates of Study: 12/11/94 - 02/13/95

Objective: To compare the extent and rate of bioavailability from diclofenac/misoprostol tablets manufactured at to tablets manufactured at

Study Design: Single-center, open-label, fasting, single-dose, crossover, replicate-design study with two treatments [test (T) and reference (R)] administered in one of two sequences: T, R and R, or R, T and T on days 1, 6 and 11, respectively.

- Test (T): diclofenac sodium 75 mg/misoprostol 200 mcg combination tablet diclofenac made in , packaged lot RCT 9722.

- Reference (R): diclofenac sodium 75 mg/misoprostol 200 mcg combination tablet diclofenac made at packaged lot RCT 9721.

Twenty-seven healthy subjects (9 female, 18 male), (mean age of 30 years) were enrolled in the study; three subjects withdrew prior to completion; 24 subjects completed the study.

Blood samples for determination of diclofenac and/or misoprostol acid plasma concentrations were obtained prior to dose and at predetermined intervals for up to 12 hours after each treatment.

Data Analysis: Noncompartmental pharmacokinetic parameter estimates for diclofenac and misoprostol acid area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (Cmax), and time to Cmax (tmax) were determined for each treatment. The ratio and corresponding 90% confidence interval (C.I.) for each parameter were used to assess the bioequivalence of the test and reference formulation and to assess the relative bioavailability of initial and replicate doses of each treatment.

Assay Method:

Results: The firm provided the following:

Relative bioavailability of diclofenac from Arthrotec 75 test and reference treatments was:

Diclofenac parameter (N=21)	Treatment means[a]		Ratio[b]	90% CI for ratio
AUC(0-∞)			100.7%	(91.3%, 111.1%)
AUC(0-lqc)	2128 (44)	2089 (30)	101.1%	(91.8%, 111.4%)
Cmax	1634 (36)	1729 (40)	100.3%	(88.4%, 113.7%)
tmax	1.3 (63)	1.7 (112)		

[a] arithmetic mean values with CV (%)
[b] geometric mean ratio
units: AUC: hr.ng/ml; Cmax: ng/ml; tmax: hr.

Relative bioavailability of misoprostol acid from test and reference treatments was:

Misoprostol acid parameter (N=24)	Treatment means[a]		Ratio[b]	90% CI for ratio
AUC(0-∞)			102.1%	(96.0%, 108.6%)
AUC(0-lqc)	207 (35)	215 (40)	98.3%	(92.0%, 104.9%)
Cmax	356 (49)	347 (54)	103.2%	(91.4%, 116.6%)
tmax	0.26 (30)	0.28 (35)		

[a] arithmetic mean values with CV (%)
[b] geometric mean ratio
units: AUC: hr.pg/ml; Cmax: pg/ml; tmax: hr.

When reference tablets were administered to the same subjects on two separate occasions, the relative bioavailability of Arthrotec 75 were:

Diclofenac parameter (N=12)	Treatment means* Repl.	Init.	Ratio Repl./Init.	90% CI for ratio
AUC(0-∞)*			96.2%	(84.9%, 109.0%)
AUC(0-lqc)*	2020.5	2172.7	93.0%	(81.7%, 105.9%)
Cmax	1549.1	1855.6	83.5%	(62.8%, 111.1%)
tmax	1.58	1.54		

* geometric mean obtained from the analysis of variance model; values were natural log-transformed prior to the analysis.
units: AUC hr.ng/ml; Cmax ng/ml; tmax hr.

Misoprostol acid parameter	Treatment means* Repl.	Init.	Ratio Repl./Init.	90% CI for ratio
AUC(0-∞)			105.1%	(91.7%, 120.4%)
AUC(0-lqc)	172.0	168.4	102.1%	(92.2%, 113.2%)
Cmax	326.8	274.8	118.9%	(104.0%, 136.1%)
tmax	0.30	0.27		

* geometric mean obtained from the analysis of variance model; values were natural log-transformed prior to the analysis.
units: AUC hr.pg/ml; Cmax pg/ml; tmax hr.

When test tablets were administered to the same subjects on two separate occasions, the relative bioavailability of Arthrotec 75 were:

Diclofenac parameter (N=10)	Treatment means* Repl.	Init.	Ratio Repl./Init.	90% CI for ratio
AUC(0-∞)			113.3%	(87.8%, 146.2%)
AUC(0-lqc)	2021.8	1799.7	112.3%	(89.3%, 141.4%)
Cmax	1576.5	1350.9	116.7%	(97.5%, 139.7%)
tmax	1.45	1.05		

* geometric mean obtained from the analysis of variance model; values were natural log-transformed prior to the analysis.
units: AUC hr.ng/ml; Cmax ng/ml; tmax hr.

Misoprostol acid parameter (N=11)	Treatment means* Repl.	Init.	Ratio Repl./Init.	90% CI for ratio
AUC(0-∞)			105.6%	(93.5%, 119.4%)
AUC(0-lqc)	165.3	155.7	106.2%	(90.6%, 124.4%)
Cmax	316.5	295.7	107.0%	(81.0%, 141.6%)
tmax	0.28	0.25		

* geometric mean obtained from the analysis of variance model; values were natural log-transformed prior to the analysis.
units: AUC hr.pg/ml; Cmax pg/ml; tmax hr.

Comments:

- The Arthrotec 75 tablets in the pivotal U.S. clinical efficacy trials (NN2-95-06-349, NN2-95-06-352) were sourced from and contained diclofenac chemical supplied by The proposed formulation is manufactured in and contains diclofenac chemical supplied by This study is to validate the change in manufacturing site and supplier of diclofenac chemical for Arthrotec 75 tablets.

- The sponsor used general linear procedure which contained terms for treatment sequence, subject (nested within sequence), period, first order carryover and treatment. The SAS output showed that the carrryover effect insignificant. This reviewer used the following SAS code to generate a mixed model analysis [random subject effect (nested within sequence), random subject*trt interaction effect, and treatment, period and sequence effects in the model are assumed fixed] to analyze the data:

```
proc mixed data=pk353d maxiter=5000 convf=1E-4;
title "Study 353 diclofenac PK data";
class seq subj per trt;
model lncmax = seq per trt/solution;
random subj trt*subj/type=simple;
lsmeans trt/cl pdiff alpha =.1;
make "diffs" out=difil;
run;
```

- The data sets analyzed by this reviewer included 21 subjects (the firm used 21 subjects in their statistical assessment), the 90% C.I.s obtained for Cmax and AUC(0-lqc) were (87.56%,

114.83%) and (90.38%, 111.17%), respectively. Subject #2, #6 and #24 were excluded in the statistical assessment. Subject #6 had Cmax of 39.10 ng/ml at 12 hours after administration of test formulation and most of other time points the concentration was zero. For subject #24, most of the concentration data were missing. However, there was no explanation why subject #2 was excluded in the analysis; the AUC value after administration of reference product was 915 h.ng/ml, which is within two times the standard deviation. This reviewer included subject #2 in the statistical assessment and from 22 subjects this reviewer obtained the following 90% C.I.s: for Cmax, (87.70%, 113.35%), for AUC(0-lqc), (88.65%, 110.58%).

Conclusion: Based on the analyses results from sponsor and this reviewer, it is concluded that the rate and extent of bioavailability of both diclofenac and misoprostol acid for tablets manufactured at were bioequivalent to those tablets manufactured at

DRUG INTERACTION BETWEEN DICLOFENAC AND MISOPROSTOL IN ELDERLY

Study No: NB2-89-02-299 Volume: 1.29 Page: 6-761

Title: Effect of Misoprostol on the Single-Dose and Multiple-Dose Pharmacokinetics of Diclofenac in Elderly Subjects

Formulations:

- Cytotec (G.D. Searle & Co.) tablets containing 200 mcg of misoprostol, commercial lot no.: 389-165
- Voltaren (Geigy Pharmaceuticals, Ardsley, New York) enteric-coated tablets containing 50 mg diclofenac sodium, commercial lot no.: 1T113098

Objective: To determine whether coadministration of misoprostol and diclofenac affected the single dose and multiple-dose pharmacokinetics of diclofenac in subjects, aged 65 years or older.

Study Design: Open-label, randomized, four-sequence, three-period crossover, replicate design study with two treatments.

Treatment A: one 50 mg diclofenac (D) tablet with breakfast on Days 1 and 5; and one 50 mg D tablet with breakfast and supper on Days 2-4.

Treatment B: one 50 mg D tablet + one 200 mcg misoprostol (M) tablet with breakfast and one 200 mcg M tablet with supper on Day 1; one 50 mg D tablet + one 200 mcg M tablet with breakfast and supper on Days 2-4; and one 50 mg D tablet + one 200 mcg M tablet with breakfast on Day 5.

Twenty-seven subjects, aged 65 years or older, were enrolled in the study. Three subjects withdrew; 24 subjects (15 male and 9 female) completed the study. Each subject received Treatment A (diclofenac) and Treatment B (diclofenac + misoprostol) once and one of the treatments (either A or B) a second time. A washout of seven days separated the study periods.

Each subject received a following standardized breakfast: one English muffin with jelly, approximately 8 ounces of skim milk and 6 ounces of orange juice) within 30 minutes of dosing on days 1 and 5.

Blood samples (5 ml each) were collected at predetermined intervals for 24 hours after the first (Day 1) and last (Day 5) doses of study medication. Additional blood samples were obtained before the morning doses on Days 3 and 4. All urine excreted during the 24-hour post-dose period on Day 1 and the 12-hour post-dose period on Day 5 was collected for later analysis if required.

Data Analysis: The following PK parameters were calculated from the Day 1 and Day 5 diclofenac plasma concentration data: AUC, Cmax, and tmax. ANOVA model containing factors for treatment, sequence, subject (nested within sequence), period, and carryover effects was used to investigate treatment group differences. The parameters AUC and Cmax were log-transformed before the analyses. Paired-t-tests comparing the day 1 and day 5 PK parameters were performed within each treatment group to determine if significant accumulation of diclofenac in plasma had occurred. Paired t-tests were also used to compare the PK parameters of subjects who had received the same treatment during two separate periods of the study.

The replicate data from the 12 subjects who received diclofenac alone during two separate study periods were used to calculate between-subject and within-subject variability in diclofenac AUC and Cmax under fed conditions. Variance components were estimated using a mixed effects linear model that included fixed effect terms for sequence, "period" and the sequence by "period" interaction, and a random effect term for subjects nested in sequence. Based on the approximation: variance $(\ln X) \approx$ [variance (X)] $\div$[mean (X)]^2, the estimated variance components were then expressed as percent coefficient of variation.

Results: The firm provided the following:

Mean (%CV) pharmacokinetic parameters of diclofenac after single and multiple doses for the two treatments are:

Parameter[a]	Voltaren + Cytotec	Voltaren	Ratio	p Value
Single dose, Day 1:				
AUC(0-24)	1508 (45)*	1982 (38)	76.08%	0.050
Cmax	1073 (54)	1452 (49)	73.90%	0.057
tmax	4.1 (18)	3.8 (26)		0.071
Multiple dose, Day 5:				
AUC(0-12)	1526 (56)	1564 (41)	97.57%	0.513
Cmax	1048 (74)	1071 (54)	97.85%	0.394
tmax	3.5 (30)	3.9 (20)		

*p=0.05, compared to Voltaren alone

[a]units: AUC = hr.ng/ml; Cmax = ng/ml; tmax = hr.

Mean AUC values on Day 1 were statistically significantly lower (p=0.05), when diclofenac was coadministered with misoprostol. Analysis of variance showed no significant treatment differences in mean Cmax and tmax values on Day 1, or in mean AUC, Cmax and Tmax values on Day 5.

Paired comparisons of Day 1 versus Day 5 pharmacokinetic parameters showed no significant differences in AUC or Cmax values within each treatment group.

Paired comparisons of the subjects who received Treatment A (diclofenac) twice showed a significant difference (p=0.011) in Day 1 tmax values. No significant differences were found for subjects who had received Treatment B (diclofenac + misoprostol) twice.

Comments:

- Since this is a replicate design study, the PK parameters were reanalyzed by this reviewer using SAS PROC MIXED [random subject effect (nested within sequence), random subject*trt interaction effect, and treatment, period and sequence effects in the model are assumed fixed]. The firm used SAS PROC GLM which contained the terms for treatment, sequence, subject (nested within sequence), period, and carryover effects to investigate treatment group differences in PK parameters. The firm's SAS output showed that the carryover effect was not significant. This reviewer found that mean AUC and Cmax values on Day 1 were statistically lower (p=0.0227 for AUC, p=0.0334 for Cmax) when diclofenac was coadministered with misoprostol as opposed to the sponsor's results which showed that 24% difference in mean AUC values on Day 1 was statistically significantly (p=0.05). However, 26% difference

in mean Cmax values on Day 1 was not statistically significant. This reviewer also found that mean AUC and Cmax values on Day 5 were not statistically different, when diclofenac was coadministered with misoprostol.

- The breakfast served in this study is: one English muffin with jelly, approximately 8 ounces of skim milk and 6 ounces of orange juice.

Conclusions: Based on the analyses results from the sponsor and this reviewer, it is concluded:

- After single dose administration in elderly subjects, diclofenac mean AUC and Cmax were decreased, when diclofenac was coadministered with misoprostol as compared to diclofenac alone. However, the multiple-dose pharmacokinetics of diclofenac 50 mg b.i.d were not affected by coadministration of misoprostol 200 mcg b.i.d.

- There is no accumulation of diclofenac in plasma in fourth day of b.i.d. dosing with either treatment regimen.

Sponsor's Labeling Claim: In a multiple-dose (b.i.d.) study of subject aged 65 years or older, the misoprostol contained in Arthrotec did not affect the pharmacokinetics of diclofenac sodium.

Labeling Comment: The firm's proposed labeling is acceptable.

MULTIPLE-DOSE BIOAVAILABILITY AND EFFECT OF FOOD ON ARTHROTEC 50

Study No.: NN2-91-02-338 **Volume:** 1.33 **Page:** 6-2488

Title: On open-label study to assess the steady-state bioavailability profile of diclofenac/misoprostol combination tablets in healthy male subjects

Objectives: To assess the bioavailability of diclofenac and misoprostol acid from diclofenac/ misoprostol combination tablets: 1) after single and multiple (b.i.d.) doses under fasting conditions; and 2) after multiple (b.i.d.) doses under fasting and nonfasting conditions.

Study Design: Open label, multiple-dose study. Twenty-four healthy male subjects, aged 22-41 years, completed the study. Each subject received one diclofenac sodium 50 mg/misoprostol 200 mcg combination tablet package lot no. ECP-1078, clinical supply I) every 12 hours for 7.5 days (total dose of 15 doses); morning dose on days 1 and 7 administered under fasting conditions; last dose on day 8 given after a standard high-fat breakfast.

Blood samples for determination of diclofenac and misoprostol acid plasma concentrations were obtained prior to and at predetermined intervals for up to eight hours after the morning dose on days 1, 7, and 8; additional predose blood samples were collected on days 5 and 6.

Data Analysis: The peak plasma concentration (Cmax), time to Cmax (tmax), and area under the curve (AUC) for diclofenac and misoprostol acid were determined for days 1, 7, and 8. Paired t-test comparisons were made of day 1 versus day 7 and day 7 versus day 8 Cmax, tmax, and AUC. Predose plasma concentrations of diclofenac and misoprostol acid on days 5, 6, 7 and 8 were examined to assess the extent of accumulation and to determine if steady-state conditions had been achieved.

Assay Method:

Results: Mean (%CV) values for diclofenac and misoprostol acid Cmax, tmax, and AUC following single and multiple doses given under fasting and nonfasting conditions were:

Parameter	Day 1 (single dose)	Day 7 (steady-state, fasted)	Day 8 (steady state, fed)
Diclofenac			
AUC(0-8), hr.ng/ml	1465 (29)	1287[a] (16)	795[b] (70)
Cmax, ng/ml	1263 (38)	999[a] (25)	754 (81)
tmax, hr	2.4 (46)	2.2 (48)	3.4 (76)
Misoprostol acid			
AUC(0-4), hr.pg/ml	281 (47)	205[a] (33)	251[b] (28)
Cmax, pg/ml	398 (58)	304 (47)	154[b] (44)
tmax, hr	0.3 (30)	0.3 (58)	0.7[b] (75)

[a] statistically significantly different ($p<0.05$) compared to day 1, calculated from paired t-test.
[b] statistically significantly different ($p<0.05$) compared to day 7, calculated from paired t-test.

The predose concentrations on days 5, 6, 7, and 8 were near or below the limit of assay sensitivity in the majority of subjects.

Conclusions: This reviewer agrees with the firm's following conclusions:

- There was essentially zero accumulation of diclofenac and misoprostol acid in plasma following repeated doses of one diclofenac/misoprostol combination tablet every 12 hours under fasting conditions.

- Compared to single-dose administration, there was a statistically significant decrease in bioavailability of diclofenac (Cmax and AUC) and misoprostol acid (AUC) following repeated doses of the combination tablet under fasting conditions; relative between-subject variability (%CV) was also reduced after multiple doses.

- The steady-state bioavailability profile was significantly altered when the combination tablet was given with food: diclofenac bioavailability (AUC) and misoprostol acid Cmax were reduced; times to peak concentration (tmax) were increased for both components; and misoprostol acid bioavailability (AUC) was increased.

Comments: The approved labeling for Voltaren states, "When diclofenac sodium is taken with food, there is a usual delay of 1 to 4.5 hours, with delays as long as 10 hours in some patients and a reduction in peak plasma levels of approximately 40%. However, the extent of diclofenac sodium absorption is not significantly affected by food intake."

The approved labeling for Cytotec states, "Maximum plasma concentrations of misoprostol are diminished when the dose is taken with food."

Sponsor's Labeling Claim for Food Effect: Food alters the multiple-dose bioavailability profile of ARTHROTEC® 50 and ARTHROTEC® 75, but this effect is similar to the effect previously reported for the two components given separately.

Labeling Comment: This reviewer obtained the following geometric mean ratios and 90% confidence intervals:

Treatment Comparison	Parameter (N=24)	Ratio	90% Confidence Interval
Fed	diclofenac AUC(0-8)	32.0%	(18.2%, 56.4%)
Fasted	diclofenac Cmax	32.4%	(17.6%, 60.0%)
	misoprostol AUC(0-4)	124.3%	(112.4%, 137.6%)
	misoprostol Cmax	49.9%	(41.6%, 59.9%)

The above information should be incorporated in the labeling.

MULTIPLE-DOSE BIOAVAILABILITY AND EFFECT OF FOOD ON ARTHROTEC 75

Study No.: NN2-93-02-347 **Volume:** 1.37 **Page:** 6-4194

Title: An open label, randomized, crossover study to assess the multiple-dose bioavailability profile of diclofenac/misoprostol combination tablets given to healthy subjects under fed and fasted conditions.

Dates of Study: 02/05/94 - 07/12/94

Objectives: The objectives of this study were :

- to assess the accumulation of diclofenac and misoprostol acid in plasma following twice-daily dosing of diclofenac/misoprostol tablets under fasted conditions;
- to compare the multiple-dose bioavailability of diclofenac from diclofenac/misoprostol tablets relative to marketed enteric-coated diclofenac tablets given under fasted conditions;
- to assess the effect of food on the bioavailability of diclofenac and misoprostol acid from diclofenac/misoprostol tablets;
- to compare the food effect on diclofenac bioavailability from diclofenac/misoprostol tablets relative to marketed enteric-coated diclofenac tablets.

Formulations:

- Diclofenac sodium 75 mg/misoprostol 200 mcg combination tablets (Arthrotec 75 packaging lot no.: RCT 9533.

- Enteric-coated diclofenac sodium 75 mg tablets (Voltaren, marketed in the U.S. Geigy Pharmaceuticals, commercial lot no.: 2JT5120), packaging lot no.: RCT 9534.

Study Design: Single-center, open-label study with two multiple-dose treatments (diclofenac/misoprostol b.i.d. and diclofenac b.i.d.) administered in a crossover manner; subjects were randomized to one of two sequences of treatment administration:

1) diclofenac/misoprostol b.i.d. on days 1 to 6 and on morning of day 7, followed by diclofenac b.i.d. on days 14 to 19 and on day 20; or

2) diclofenac b.i.d. on days 1 to 6 and on morning of day 7, followed by diclofenac/misoprostol b.i.d. on days 14 to 19 and on morning of day 20.

The morning dose on days 6 and 19 was given under fasted conditions (overnight fast followed by four hour postdose fast); the morning dose on days 7 and 20 was given under fed conditions (standard high-fat [>50g fat] breakfast within 30 minutes prior to dose).

Twenty-eight healthy volunteers (20 males, 8 females), were enrolled in the study; four subjects withdrew prior to study completion; 24 subjects completed the study.

Blood samples for diclofenac and, if appropriate, misoprostol acid assay were collected prior to dose on days 1, 4, 5, 6, 7, 14, 17, 18, 19 and 20 and at predetermined times for 12 hours after the morning dose on days 6, 7, 19 and 20.

Data Analysis: The following noncompartmental pharmacokinetic parameters ware determined for days 6, 7, 19 and 20: area under the concentration-time curve [AUC(0-12) for diclofenac, AUC(0-4) for misoprostol acid]; maximum observed plasma concentration (Cmax); time to Cmax (tmax). The ratio and corresponding 90% confidence interval for each parameter were used to assess the relative bioavailability of the two treatments under fasted conditions; additional statistical analyses were performed to assess the effect of food on diclofenac and misoprostol acid bioavailability from Arthrotec 75, and to compare the food effect on diclofenac bioavailability from Arthrotec 75 and from marketed Voltaren.

Assay Method:

Results: The firm provided the following:

Multiple-dose Relative Bioavailability

Under fasted conditions, mean (%CV) values for diclofenac Cmax, tmax, and AUC following multiple doses of Arthrotec 75 b.i.d. and Voltaren 75 mg b.i.d. are:

Treatment (N=22)	Cmax (ng/ml)	tmax (hr)	AUC(0-12) (hr.ng/ml)
Arthrotec 75 b.i.d.	1807 (33)	1.9 (100)	2526 (26)
Voltaren b.i.d.	2203 (53)	2.5 (42)	2762 (39)

The geometric mean ratio and the associated 90% confidence interval for AUC and Cmax are:

Treatment Comparison	Diclofenac Parameter (N=22)	Ratio	90% Confidence Interval
Arthrotec 75	AUC(0-12)	93.2%	(83.4%, 104.1%)
Voltaren	Cmax	86.5%	(71.9%, 103.9%)

The 14% difference between fasted mean diclofenac Cmax values was not statistically significant (p=0.187).

Under fed conditions, mean (%CV) values for diclofenac Cmax, tmax, and AUC following multiple doses of Arthrotec 75 b.i.d. and Voltaren 75 mg b.i.d. are:

Treatment (N=22)	Cmax (ng/ml)	tmax (hr)	AUC(0-12) (hr.ng/ml)
Arthrotec 75 b.i.d.	1110 (46)	4.0 (46)	1968 (28)
Voltaren b.i.d.	986 (81)	5.8 (67)	1971 (78)

The geometric mean ratio and the associated 90% confidence interval for AUC and Cmax are:

Treatment Comparison	Diclofenac Parameter (N=22)	Ratio	90% Confidence Interval
Arthrotec 75	AUC(0-12)	137.4%	(96.3%, 196.2%)
Voltaren	Cmax	143.5%	(97.5%, 211.1%)

Under fed conditions, mean diclofenac AUC(0-12) and Cmax values for Arthrotec 75 were 37% and 44% higher than those for Voltaren given with food, respectively.

Effect of Food on multiple-dose bioavailability

Mean (%CV) values for diclofenac and misoprostol acid Cmax, tmax, and AUC from Arthrotec 75 b.i.d. under fasted and fed conditions are:

Arthrotec 75 Treatment (N=22)	Diclofenac Cmax (ng/ml)	tmax (hr)	AUC(0-12) (hr.ng/ml)
Fasted	1807 (33)	1.9 (100)	2526 (26)
Fed	1110* (46)	4.0* (46)	1968 (28)

Arthrotec 75 Treatment (N=24)	Misoprostol acid Cmax (pg/ml)	tmax (hr)	AUC(0-4) (hr.pg/ml)
Fasted	301 (60)	0.29 (23)	178 (54)
Fed	117* (48)	0.80* (90)	188 (48)

*statistically significantly different ($p<0.05$) compared to fasted conditions.

Compared to fasted conditions, administration of Arthrotec 75 with a high-fat meal resulted in statistically significant decreases in diclofenac and misoprostol acid Cmax and significant increases in tmax; diclofenac AUC was diminished and the average misoprostol acid AUC was increased, however, the differences between fed and fasted AUCs were not statistically significant.

Under fasted conditions, there was no appreciable accumulation of diclofenac in plasma with diclofenac /misoprostol b.i.d.; misoprostol acid predose concentrations were zero.

Comments:

- Diclofenac Cmax, tmax and AUC(0-12) were not determined for subjects 18 and 923 and they were excluded from the statistical analysis of diclofenac data since most of the diclofenac concentration values of those subjects were missing.

- This reviewer reanalyzed the diclofenac concentration data from this study and obtained similar pharmacokinetic parameters and statistical results as sponsor's.

Comments: The approved labeling for Voltaren states, "When diclofenac sodium is taken with food, there is a usual delay of 1 to 4.5 hours, with delays as long as 10 hours in some patients and a reduction in peak plasma levels of approximately 40%. However, the extent of diclofenac sodium absorption is not significantly affected by food intake."

The approved labeling for Cytotec states, "Maximum plasma concentrations of misoprostol are diminished when the dose is taken with food."

Sponsor's Labeling Claim for Food Effect: Food alters the multiple-dose bioavailability profile of ARTHROTEC®50 and ARTHROTEC® 75, but this effect is similar to the effect previously reported for the two components given separately.

Labeling Comment: This reviewer obtained the following geometric mean ratios and 90% confidence intervals for Arthrotec 75:

Treatment Comparison	Parameter (N=24)	Ratio	90% Confidence Interval
Fed	diclofenac AUC(0-12)	80.4%	(65.2%, 99.1%)
Fasted	diclofenac Cmax	58.1%	(46.7%, 72.2%)
	misoprostol AUC(0-4)	106.0%	(97.2%, 115.5%)
	misoprostol Cmax	41.1%	(34.9%, 48.6%)

The above information should be incorporated in the labeling.

APPEARS THIS WAY
ON ORIGINAL

COMPARATIVE BIOAVAILABILITY OF ARTHROTEC 50 AND ARTHROTEC 75

Study No.: NN2-94-02-350 **Volume:** 1.37 **Page:** 6-4562

Title: An Open Label, Randomized, Crossover Study to Compare the Bioavailability of Diclofenac from Multiple Doses of Diclofenac/Misoprostol Combination Tablets Given b.i.d. and t.i.d. to Healthy Subjects

Dates of Study: 6 March 1994 - 7 June 1994

Formulations:

- Diclofenac sodium 75 mg/misoprostol 200 mcg combination tablet, packaging lot no.: RCT 9553.
- Diclofenac sodium 50 mg /misoprostol 200 mcg combination tablet, Packaging lot no.: RCT 9554.

Study Design: Single-center, open-label study with two multiple-dose treatments (one diclofenac 75 mg/misoprostol 200 mcg tablet twice-daily [b.i.d.] and one diclofenac 50 mg/misoprostol 200 mcg tablet three-times-daily [t.i.d.]) administered in a crossover manner; subjects were randomized to one of two sequences of treatment administration:

1) t.i.d. on days 1-6, followed by b.i.d. on days 15-20; or
2) b.i.d. on days 1-6, followed by t.i.d. on days 15-20.

Twenty-nine healthy volunteers (22 males, 7 females), (mean 29 years) were enrolled in the study; five subjects withdrew prior to study completion; 24 subjects completed the study. Blood samples for diclofenac assay were collected prior to dose on days 1, 4, 5, 6, 15, 18, 19 and 20 and at predetermined times for 24 hours after the A.M. dose on days 6 and 20.

Data Analysis: From each day 6 and day 20 diclofenac plasma concentration-time curve, the following noncompartmental pharmacokinetic parameter were determined: AUC(0-24), area under the concentration-time curve from time 0 to 24 hours postdose; Cmax(A.M.), maximum observed plasma concentration during the first dose interval following the A.M. dose (i.e., from time 0 to 8 hours postdose for t.i.d. treatment and from time 0 to 12 hours postdose for b.i.d. treatment); tmax(A.M.), the time from the A.M. dose to Cmax(A.M.); Cmax, the maximum observed plasma concentration during the 24 hour internal after the A.M. dose; tmax, the time from A.M. dose to Cmax. The ratio and corresponding 90% confidence internal (CI) for each parameter were used to assess the relative bioavailability of diclofenac from the b vs. t.i.d. treatments.

Assay Method:

Results: The relative bioavailability of diclofenac from Arthrotec 75 b.i.d. vs. Arthrotec 50 t.i.d. treatments was:

Diclofenac parameter	Treatment mean* (%CV) b.i.d. (N=24)	t.i.d. (N=23)^	Ratio b.i.d./t.i.d.	90% CI for ratio
AUC(0-24)	4424 (31)	4738 (42)	95.2%	(84.6%, 107.2%)
Cmax(A.M.)	1520 (33)	1017 (32)	150.7%	(128.6%, 176.5%)
tmax(A.M.)	2.3 (98)	1.3 (52)		

* Arithmetic mean values.
^: N=22 for AUC(0-24), Cmax and tmax.
units: AUC hr.ng/ml; Cmax ng/ml, tmax hr.

Conclusions: This reviewer agrees with the firm's following conclusions:

- The extent of diclofenac bioavailability (AUC) at steady state from 150 mg total daily doses of diclofenac was equivalent when given as Arthrotec 75 b.i.d. and Arthrotec 50 t.i.d..

- The average peak diclofenac plasma concentration for the morning dose [Cmax(A.M.)] was 51% higher for diclofenac 75 mg/misoprostol 200 mcg tablets than for diclofenac 50 mg/misoprostol 200 mcg tablets.

Comments: In this study, misoprostol acid concentrations were not measured.

EFFECT OF AGE AND GENDER ON THE APPARENT ORAL CLEARANCE OF DICLOFENAC AND MISOPROSTOL

Document No: NN2-95-07-822

Searle provided the results of analysis of age and gender effect as per the Agency's information request during the Pre-NDA meeting between the Agency and the firm.

Data Analysis: Diclofenac and misoprostol acid plasma concentration data from six bioavailability studies with Arthrotec 50 or 75 (Study No. NN2-91-02-332, NN2-91-02-343, NN2-93-02-345-01, NN2-93-02-346, NN2-94-02-353, NN2-95-02-354) were analyzed in the current analysis. Apparent oral clearances for diclofenac and misoprostol were calculated as dose/AUC(0-lqc) and, if available, dose/AUC(0-∞). Since study Nos. NN2-91-02-343, NN2-93-02-345-01 and NN2-94-02-353 were replicate design studies; approximately half of the subjects received the treatments twice during two separate study periods and consequently, had two AUCs for a given treatment. An average clearance value was used in the current analysis.

The analyses used a general linear model with the clearance value as the dependent variable and study, age and gender as independent factors.

Results: The firm provided the following table which summarized the mean apparent oral clearance values for diclofenac and misoprostol by study and gender.

TABLES

Table 1. Mean diclofenac and misoprostol clearances by study and gender.

Means by Sample Type, Study and Sex for Clearance [LQC or INF] [1/hr x 10e-3]

SAMPLE TYPE	STUDY	Clearance (LQC) MEAN SEX F	Clearance (LQC) MEAN SEX M	Clearance (LQC) N SEX F	Clearance (LQC) N SEX M	Clearance (INF) MEAN SEX F	Clearance (INF) MEAN SEX M	Clearance (INF) N SEX F	Clearance (INF) N SEX M
DICLOFENAC	NN2-91-02-332-00	0.0424		36		0.0418		36	
	NN2-91-02-343-00	0.0374		24		0.0372		24	
	NN2-93-02-345-01	0.0348		21				0	
	NN2-93-02-346-00	0.0263	0.0340	7	28			0	0
	NN2-94-02-353-00	0.0388	0.0382	7	18	0.0392	0.0369	5	18
	NN2-95-02-354-00	0.0893	0.0711	7	23	0.0498	0.0673	4	16
	All Studies	0.0548	0.0429	21	150	0.0439	0.0442	9	91
MISOPROSTOL	STUDY								
	NN2-91-02-332-00		1.1347		36				0
	NN2-91-02-343-00	1.3395		24		1.3292		24	
	NN2-93-02-345-01	1.0012		24		1.0036		24	
	NN2-93-02-346-00	1.1232	1.4768	7	28	1.0177	1.3102	7	27
	NN2-94-02-353-00	1.1368	1.3273	7	17	0.9480	1.0774	6	14
	NN2-95-02-354-00	1.3661	1.9408	7	23	1.0828	1.4693	4	13
	All Studies	1.2088	1.3533	21	153	1.0084	1.2308	17	102

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Conclusion: The results of analyses of data from six bioavailability studies with Arthrotec showed no statistically significant effects ($p \geq 0.101$) on diclofenac apparent oral clearances attributable to age or gender. For misoprostol there was a borderline significance ($p=0.051$) in the apparent clearance between males and females. However, it is not known whether there is a gender difference in the apparent clearance for misoprostol when the model included the body weight as a covariate.

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pages of trade secret and/or confidential commercial information

GENERAL COMMENTS (to be sent to the firm):

1. **With regards to Study -332:**

There is a discrepancy between AUC values for diclofenac determined by this reviewer and those reported from the sponsor. However, this reviewer obtained similar 90% C.I.s for diclofenac as sponsor's. Similarly, there is a discrepancy between misoprostol acid AUC values. The firm is recommended to check the data.

The sponsor's data showed that the mean AUC(0-4) and Cmax values for misoprostol acid from ARTHROTEC 50 Study -332) were 235 (CV, 41%) pg.hr/ml and 441 (31%) pg/ml, respectively. And those from ARTHROTEC 75 Study -346) were 177 (27%) pg.hr/ml and 304 (36%) pg/ml, respectively. The amount of misoprostol contained in ARTHROTEC 50 and 75 are the same, which is 200 mcg. In comparison of those parameters, the bioavailability of misoprostol acid from ARTHROTEC 50 Study -332) seems higher.

The following table shows the mean (CV, %) misoprostol acid AUC and Cmax values across studies:

Study No.	Formulation	Mean AUC(0-4)	Mean Cmax
-332		235 (41%)	441 (31%)
-346		177 (27%)	304 (36%)
-343		196 (62%)	348 (76%)
		178 (53%)	322 (74%)
-345	product	157 (33%)	295 (37%)
	Arthrotec	205 (40%)	374 (43%)
-354	product	134 (40%)	234 (34%)
	product	130 (46%)	221 (55%)
	Arthrotec	147 (51%)	234 (41%)
-338		281 (47%)	398 (58%)
-353	product	207 (35%)	356 (49%)
		215 (40%)	347 (54%)
	average	189	323

The firm needs to explain the relatively high misoprostol acid plasma levels seen in Study -332.

The firm is recommended to replace PK parameters of Arthrotec 50 in the labeling with more suitable values reflective of the population as a whole.

2. The results of analyses of data from six bioavailability studies with Arthrotec showed no statistically significant effects ($p \geq 0.101$) on diclofenac apparent oral clearances attributable to age or gender. For misoprostol there was a borderline significance ($p=0.051$) in the apparent clearance between males and females. However, it is not known whether there is still a gender difference in the apparent clearance for misoprostol when the model included the body weight as a covariate. The firm is recommended to do gender analysis including body weight as a covariate. If the result is still significant, then that information should be included in the labeling, if thought to be clinically relevant.

3. The following dissolution conditions and specifications are recommended for Arthrotec:

Diclofenac

4. **With regards to Study -316:**

The ANOVA model used by the sponsor included terms for sequence, subject nested within sequence, period, first order carryover and treatment as factors. This reviewer reanalyzed the data using the ANOVA model which contained terms for treatment, period, sequence and subject (nested within the sequence) and obtained the similar results as sponsor's; the diclofenac/placebo tablets were bioequivalent to the marketed Voltaren (U.S.) in terms of diclofenac AUC and Cmax.

5. **With regards to Study -345:**

For the assessment of bioequivalence, the sponsor used SAS PROC GLM which contained terms for sequence, subject (nested within sequence), period, first order carryover and treatment as factors. Since this is a replicate design study, this reviewer reanalyzed the diclofenac data using SAS PROC MIXED (random subject effect, random subject*treatment interaction, all other effects in the model are assumed fixed) and obtained the 90% confidence intervals of (74.9%, 106.8%) for Cmax and (89.6%, 107.8%) for AUC(0-lqc), respectively. In the statistical analyses, subject # 104, 105, 109, 111 and 124 were not included since those subjects had insufficient diclofenac concentration data (i.e., values missing and/or less than assay sensitivity limit).

6. With regards to Study -354:

The firm provided AUC(0-∞) values for diclofenac from only 20 subjects. This reviewer recalculated AUC(0-∞); for Canadian, proposed product and proposed product formulations, 28, 30 and 29 subjects were included in the calculations of diclofenac AUC(0-∞). The statistical model used by this reviewer included sequence, treatment, period and subject (within sequence) as factors, whereas the ANOVA model used by sponsor included the terms for sequence, subject within sequence, treatment and first order carryover. This reviewer obtained the following: all the 90 % C.I. for diclofenac AUC(0-∞) passed the bioequivalency criteria. In comparison of the proposed product to Canadian Arthrotec, this reviewer obtained the 90 % C.I. for diclofenac Cmax with 90% C.I.=73.9-107.9%; bioequivalency was not established.

7. With regards to Study -353:

The sponsor used general linear procedure which contained terms for treatment sequence, subject (nested within sequence), period, first order carryover and treatment. The SAS output showed the carryover effect insignificant. This reviewer used the following SAS code to generate a mixed model analysis [random subject effect (nested within sequence), random subject*treatment interaction effect, and treatment, period and sequence effects in the model are assumed fixed] to analyze the diclofenac data. The data sets analyzed by this reviewer included 21 subjects (the firm used 21 subjects in their statistical assessment), the 90% C.I.s obtained for Cmax and AUC(0-lqc) were (87.56%, 114.83%) and (90.38%, 111.17%), respectively. Subject #2, #6 and #24 were excluded in the statistical assessment. Subject #6 had Cmax of 39.10 ng/ml at 12 hours after administration of test formulation and most of other time points the concentration was zero. For subject #24, most of the concentration data were missing. However, there was no explanation why subject #2 was excluded in the analysis; the AUC value after administration of reference product was 915 h.ng/ml, which is within two times the standard deviation. This reviewer included subject #2 in the statistical assessment and from 22 subjects this reviewer obtained the following 90% C.I.s: for Cmax, (87.70%, 113.35%), for AUC(0-lqc), (88.65%, 110.58%), respectively.

8. With regards to Study -299:

Since this is a replicate design study, the diclofenac PK parameters were reanalyzed by this reviewer using SAS PROC MIXED [random subject effect (nested within sequence), random subject*treatment interaction effect, and treatment, period and sequence effects in the model are assumed fixed]. The firm used SAS PROC GLM which contained the terms for treatment, sequence, subject (nested within sequence), period, and carryover effects to investigate treatment group differences in PK parameters. The firm's SAS output showed that the carryover effect was not significant. This reviewer found that mean AUC and Cmax values on Day 1 were statistically lower ($p=0.0227$ for AUC, $p=0.0334$ for Cmax) when diclofenac was coadministered with misoprostol as opposed to the sponsor's results which showed that 24% difference in mean AUC values on Day 1 was statistically significantly ($p=0.05$), and 26% difference in mean Cmax values on Day 1 was not statistically significant. This reviewer found that mean AUC and Cmax values on Day 5 were not statistically different, when diclofenac was coadministered with misoprostol.

9. This reviewer obtained the following geometric mean ratios and 90% confidence intervals for the food effect studies (Study -338 and -347):

Study -338 (Arthrotec 50)

Treatment Comparison	Parameter (N=24)	Ratio	90% Confidence Interval
Fed	diclofenac AUC(0-8)	32.0%	(18.2%, 56.4%)
Fasted	diclofenac Cmax	32.4%	(17.6%, 60.0%)
	misoprostol AUC(0-4)	124.3%	(112.4%, 137.6%)
	misoprostol Cmax	49.9%	(41.6%, 59.9%)

Study -347 (Arthrotec 75)

Treatment Comparison	Parameter (N=24)	Ratio	90% Confidence Interval
Fed	diclofenac AUC(0-12)	80.4%	(65.2%, 99.1%)
Fasted	diclofenac Cmax	58.1%	(46.7%, 72.2%)
	misoprostol AUC(0-4)	106.0%	(97.2%, 115.5%)
	misoprostol Cmax	41.1%	(34.9%, 48.6%)

The above information should be incorporated in the labeling.

In order to obtain an idea of the food effect, these studies should be conducted as a single dose study.

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DRAFT

Labeling