

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 tablets in 24 healthy subjects is: and reference

Parameter	Treatment Means		Ratio Test/Ref.	90% C.I. for Ratio
	Test	Reference		
<u>AUC(0-∞)</u> <sup>a</sup> (hr.ng/ml)	1365.0	1409.1	96.9%	(91.2%, 102.9%)
<u>C<sub>max</sub></u> <sup>a</sup> (ng/ml)	1004.2*	1146.4	87.6%	(80.1%, 95.8%)
<u>t<sub>max</sub></u> <sup>b</sup> (hr)	1.69	2.28	74.2%	

<sup>a</sup> geometric least squares means

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

<sup>a</sup> geometric least squares means

<sup>b</sup> 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.

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## 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 (C<sub>max</sub>), and time to C<sub>max</sub> (t<sub>max</sub>) were determined for each treatment. C<sub>max</sub> and AUC values were log-transformed before analyses.

C<sub>max</sub> 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		Ratio Test/Ref.	90% C.I. for Ratio
	Test	Reference		
<u>AUC(0-lgc)<sup>a</sup></u> (hr.ng/ml)	1432.6	1447.9	98.9%	(91.2%, 107.4%)
<u>C<sub>max</sub><sup>a</sup></u> (ng/ml)	1052.8	1176.7	89.5%	<u>(77.5%, 103.3%)</u>
<u>t<sub>max</sub><sup>b</sup></u> (hr)	1.17	2.08	56.3%	

<sup>a</sup> geometric least squares means

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

<sup>a</sup> geometric least squares means

<sup>b</sup> 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  $AUC(0-\infty)$ ,  $AUC(0-1qc)$  and  $C_{max}$ . 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 [ $AUC(0-1qc)$ ], but not for  $C_{max}$ .
- The bioequivalence of the misoprostol of the test and reference tablets was demonstrated for extent of misoprostol acid bioavailability [ $AUC(0-\infty)$ ], but not for  $C_{max}$ .

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## 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 manufactured at diclofenac 50 mg misoprostol 200 mcg,
- Proposed manufactured at diclofenac 50 mg misoprostol 200 mcg,
- 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.  $C_{max}$  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:

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/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/ 10/11/96

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)

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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 Product	AUC(0-lqc)	99.1%	(87.5%, 112.4%)
	AUC(0-∞)*	104.3%	(94.1%, 115.7%)
	Cmax	102.9%	(83.4%, 127.0%)

\* N=20 for AUC(0-∞)

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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 supplied by	Product diclofenac	134 (40)	234 (34)	0.31 (33)
Proposed supplied by	Product diclofenac	130 (46)	221 (55)	0.33 (32)
Proposed supplied by	Product 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 Product	AUC(0-lqc)	94.3%	(83.9%, 106.1%)
	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  $AUC(0-\infty)$  values for diclofenac from only 20 subjects. This reviewer recalculated  $AUC(0-\infty)$  for diclofenac; for Canadian, proposed and proposed product formulations, 28, 30 and 29 subjects were included in the calculations of diclofenac  $AUC(0-\infty)$ . It was found that  $AUC(0-lqc)$  contributed more than 90% of  $AUC(0-\infty)$ . 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  $AUC(0-\infty)$  obtained from 20 subjects, passed.  $C_{max}$  with 90% C.I. = 79.0-120.3% marginally missed establishing bioequivalence. This reviewer obtained the following: the 90% C.I. for  $AUC(0-\infty)$  passed the bioequivalency criteria;  $C_{max}$  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  $AUC(0-\infty)$  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  $AUC(0-\infty)$ . However, the rate of absorption in terms of  $C_{max}$  was not equivalent.

Misoprostol acid was shown to be bioequivalent both in terms of the extent of absorption [ $AUC(0-\infty)$  and  $AUC(0-lqc)$ ] and the rate of absorption ( $C_{max}$ ).

product

Diclofenac was shown to be bioequivalent both in terms of the extent of absorption [ $AUC(0-\infty)$ ] and the rate of absorption ( $C_{max}$ ).

Misoprostol acid equivalence was established in terms of  $AUC(0-\infty)$ ,  $AUC(0-lqc)$ , but not for  $C_{max}$ .

product vs. product

Equivalence was shown for the extent of diclofenac absorption in terms of AUC(0-1qc) 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(0-1qc) and AUC(0-∞), but not for Cmax.

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**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 (C<sub>max</sub>), and time to C<sub>max</sub> (t<sub>max</sub>) 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)	<u>Treatment means</u> <sup>a</sup>	Ratio <sup>b</sup>	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)		

<sup>a</sup> arithmetic mean values with CV (%)

<sup>b</sup> 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)	<u>Treatment means</u> <sup>a</sup>	Ratio <sup>b</sup>	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)		

<sup>a</sup> arithmetic mean values with CV (%)

<sup>b</sup> 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)	<u>Treatment means*</u>		Ratio Repl./Init.	90% CI for ratio
	Repl.	Init.		
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	<u>Treatment means*</u>		Ratio Repl./Init.	90% CI for ratio
	Repl.	Init.		
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)	<u>Treatment means*</u>		Ratio Repl./Init.	90% CI for ratio
	Repl.	Init.		
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*		Ratio Repl./Init.	90% CI for ratio
	Repl.	Init.		
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 carryover 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 \_\_\_\_\_

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## **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, C<sub>max</sub>, and t<sub>max</sub>. 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 C<sub>max</sub> 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 C<sub>max</sub> 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)]<sup>2</sup>, the estimated variance components were then expressed as percent coefficient of variation.

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Results: The firm provided the following:

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

Parameter <sup>a</sup>	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

<sup>a</sup>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.

**APPEARS THIS WAY  
ON ORIGINAL**

## 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 ( $C_{max}$ ), time to  $C_{max}$  ( $t_{max}$ ), 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  $C_{max}$ ,  $t_{max}$ , 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 C<sub>max</sub>, t<sub>max</sub>, 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)
<b><u>Diclofenac</u></b>			
AUC(0-8), hr.ng/ml	1465 (29)	1287 <sup>a</sup> (16)	795 <sup>b</sup> (70)
C <sub>max</sub> , ng/ml	1263 (38)	999 <sup>a</sup> (25)	754 (81)
t <sub>max</sub> , hr	2.4 (46)	2.2 (48)	3.4 (76)
<b><u>Misoprostol acid</u></b>			
AUC(0-4), hr.pg/ml	281 (47)	205 <sup>a</sup> (33)	251 <sup>b</sup> (28)
C <sub>max</sub> , pg/ml	398 (58)	304 (47)	154 <sup>b</sup> (44)
t <sub>max</sub> , hr	0.3 (30)	0.3 (58)	0.7 <sup>b</sup> (75)

<sup>a</sup> statistically significantly different ( $p < 0.05$ ) compared to day 1, calculated from paired t-test.

<sup>b</sup> 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 (C<sub>max</sub> 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 C<sub>max</sub> were reduced; times to peak concentration (t<sub>max</sub>) 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:

<u>Treatment Comparison</u>	<u>Parameter (N=24)</u>	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Fed</u>	diclofenac AUC(0-8)	32.0%	(18.2%, 56.4%)
<u>Fasted</u>	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.

**APPEARS THIS WAY  
ON ORIGINAL**

## 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 were 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 ( $C_{max}$ ); time to  $C_{max}$  ( $t_{max}$ ). 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 C<sub>max</sub>, t<sub>max</sub>, and AUC following multiple doses of Arthrotec 75 b.i.d. and Voltaren 75 mg b.i.d. are:

<u>Treatment</u> (N=22)	<u>C<sub>max</sub></u> (ng/ml)	<u>t<sub>max</sub></u> (hr)	<u>AUC(0-12)</u> (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 C<sub>max</sub> are:

<u>Treatment Comparison</u>	<u>Diclofenac Parameter</u> (N=22)	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Arthrotec 75</u>	AUC(0-12)	93.2%	(83.4%, 104.1%)
<u>Voltaren</u>	C <sub>max</sub>	86.5%	(71.9%, 103.9%)

The 14% difference between fasted mean diclofenac C<sub>max</sub> values was not statistically significant (p=0.187).

Under fed conditions, mean (%CV) values for diclofenac C<sub>max</sub>, t<sub>max</sub>, and AUC following multiple doses of Arthrotec 75 b.i.d. and Voltaren 75 mg b.i.d. are:

<u>Treatment</u> (N=22)	<u>C<sub>max</sub></u> (ng/ml)	<u>t<sub>max</sub></u> (hr)	<u>AUC(0-12)</u> (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:

<u>Treatment Comparison</u>	<u>Diclofenac Parameter (N=22)</u>	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Arthrotec 75</u>	AUC(0-12)	137.4%	(96.3%, 196.2%)
<u>Voltaren</u>	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:

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

<u>Arthrotec 75 Treatment (N=24)</u>	<u>Misoprostol acid Cmax (pg/ml)</u>	<u>tmax (hr)</u>	<u>AUC(0-4) (hr.pg/ml)</u>
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:

<u>Treatment Comparison</u>	<u>Parameter (N=24)</u>	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Fed</u>	diclofenac AUC(0-12)	80.4%	(65.2%, 99.1%)
<u>Fasted</u>	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; C<sub>max</sub>(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); t<sub>max</sub>(A.M.), the time from the A.M. dose to C<sub>max</sub>(A.M.); C<sub>max</sub>, the maximum observed plasma concentration during the 24 hour interval after the A.M. dose; t<sub>max</sub>, the time from A.M. dose to C<sub>max</sub>. The ratio and corresponding 90% confidence interval (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)		Ratio b.i.d./t.i.d.	90% CI for ratio
	b.i.d. (N=24)	t.i.d. (N=23)^		
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.

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## **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  $\text{dose}/\text{AUC}(0-l_{qc})$  and, if available,  $\text{dose}/\text{AUC}(0-\infty)$ . 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.

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Arthrotec®  
 Age and Gender Effect on Apparent Oral  
 Clearance of Diclofenac and Misoprostol

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 NN2-95-07-822  
 29 Nov 1995

TABLES

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

SAMPLE TYPE	STUDY	Clearance (LOC)				Clearance (INT)			
		MEAN		N		MEAN		N	
		F	M	F	M	F	M	F	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	
	NN2-94-02-353-00	0.0389	0.0382	7	18	0.0392	0.0389	9	
	NN2-95-02-354-00	0.0893	0.0711	7	23	0.0488	0.0673	4	
	All Studies	0.0548	0.0429	21	150	0.0439	0.0462	9	
MISOPROSTOL	NN2-91-02-332-00	1.1347		36				0	
	NN2-91-02-343-00	1.3395		29		1.3292		24	
	NN2-93-02-345-01	1.0012		24		1.0936		24	
	NN2-93-02-346-00	1.1232	1.4768	7	29	1.0177	1.3102	7	
	NN2-94-02-353-00	1.1369	1.3273	7	17	0.9480	1.0774	6	
	NN2-95-02-354-00	1.3661	1.9408	7	23	1.0828	1.4693	4	
	All Studies	1.2088	1.3533	21	153	1.0084	1.2308	17	

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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.

**APPEARS THIS WAY  
ON ORIGINAL**

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5

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 significant ( $p=0.05$ ), 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)

<u>Treatment Comparison</u>	<u>Parameter (N=24)</u>	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Fed</u> <u>Fasted</u>	diclofenac AUC(0-8)	32.0%	(18.2%, 56.4%)
	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)

<u>Treatment Comparison</u>	<u>Parameter (N=24)</u>	<u>Ratio</u>	<u>90% Confidence Interval</u>
<u>Fed</u> <u>Fasted</u>	diclofenac AUC(0-12)	80.4%	(65.2%, 99.1%)
	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.

2 Page(s) Redacted

DRAFT  
Labeling

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020607**

**ADMINISTRATIVE DOCUMENTS**

**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:** December 12, 1997  
**FROM:** Brian Strongin, Regulatory Health Project Manager  
**SUBJECT:** NDA 20-607, Arthrotec, Marked-Up Draft Labeling  
**TO:** NDA 20-607

The attached marked-up draft labeling is based on the revised draft labeling submitted September 29, 1997 by the firm. All Agency comments arose from an internal labeling meeting December 4, 1997 and a meeting with Searle December 11, 1997. Attendees of both meetings are listed below. Since agreement with the firm was reached in the December 11, 1997 meeting, this labeling will be the basis for the "Approval on Draft" action to be taken.

**December 4, 1997**

Paula Botstein, M.D.	Director, ODE III
Bronwyn Collier	Special Assistant to the Director ODE III
Kathy Robie-Suh, M.D., Ph.D.	Medical Officer, HFD-180
Brian Strongin	Regulatory Health Project Manager, HFD-180
John Hyde, M.D., Ph.D.	Medical Team Leader, HFD-550
James Witter, M.D., Ph.D.	Medical Officer, HFD-180
Sharon Schmidt	Regulatory Health Project Manager, HFD-550

**December 11, 1997**

FDA

Paula Botstein, M.D.	Director, ODE III
Michael Weintraub, M.D.	Director, ODE V
Bronwyn Collier	Special Assistant to the Director ODE III
Kathy Robie-Suh, M.D., Ph.D.	Medical Officer, HFD-180
Brian Strongin	Regulatory Health Project Manager, HFD-180
James Witter, M.D., Ph.D.	Medical Officer, HFD-180
Sharon Schmidt	Regulatory Health Project Manager, HFD-550

NDA 20-607

Page 2

Searle

R. Spivey, Pharm D., Ph.D.  
P. East  
J. Lefkowitz, M.D.  
P. Hamelin  
R. Bogomolny, Esq.  
C. Wertjes, Esq.

V.P., Worldwide Regulatory Affairs  
Associate Director, Regulatory Affairs  
Director, Medical Affairs  
V.P., U.S. Marketing  
General Counsel  
Assistant General Counsel

cc:

NDA 20-607/Division File  
HFD-180/Kathy Robie-Suh, M.D., Ph.D.  
HFD-550/Sharon Schmidt

**APPEARS THIS WAY  
ON ORIGINAL**

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DRAFT  
LABELING

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

FEB - 1 1996

Application Number: 20-607

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

Sponsor: G.D. Searle & Company

Material Reviewed

Submission Date(s): December 22, 1995

Receipt Date(s): December 26, 1995

**Background and Summary Description:** This application was submitted for the acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in patients at risk of developing nonsteroidal anti-inflammatory drug (NSAID)-induced gastroduodenal ulcers.

G.D.Searle's Cytotec brand of misoprostol (NDA 19-268) has been approved for the prevention of NSAID-induced gastric ulcer in patients at high risk of complications from gastric ulcers since December 27, 1988.

An enteric coating was later developed for the market formulation.

The application contains seven pivotal studies; four in support of the osteoarthritis indication (Studies 349, 296, 289, and 321), and three in support of the rheumatoid arthritis indication (Studies 352, 289 and 292). Studies 349 and 352 use an Arthrotec formulation with the enteric coating; the other pivotal studies used the enteric coating. While

pivotal rheumatoid arthritis Study # 352 and osteoarthritis Study # 349 were conducted in the U.S., the other pivotal studies were multinational. All studies utilize a factorial design, and are randomized, parallel group, double blind, and multicenter, with the U.S. studies including a placebo arm. The studies were designed to compare the efficacy of Arthrotec to diclofenac and, in the U.S. studies, the efficacy of diclofenac was also compared to placebo. In addition, in four (RA Study #289 and OA Studies #349, 321, and 296) studies utilizing endoscopies, gastrointestinal mucosal damage associated with Arthrotec was compared to that associated with a diclofenac/placebo combination.

#### Review

1. Case report tabulations, as described on page 20 of the February 1987 edition of the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications", were not provided on a per-patient basis. Data was separated into multiple tables, i.e. "Patient Characteristics", "Efficacy Listings", "Adverse Events", and grouped within tables by investigator.
2. One case report form for pivotal Study #292 was in French (Volume 1.267, page 12-26,082). Although the case report form and the entries were both in French, an English translation of the blank case report form was provided in Appendix A.1 to the study report for Study #292 (Volume 1.83, page 8-15,741).
3. The table of all clinical studies, as described on page 13 of the July 1988 edition of the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application", deviated from the guideline in these respects:
  - A. Lacked the starting date for the study
  - B. Lacked the location of case report forms and case report tabulations

Case report tabulations are included as an appendix to each study report with duplicates provided in Section 11 of the application. Case report forms are listed by study number

in the Table of Contents to the Application.

4. Investigator CVs for Study #298 ("Misoprostol/Diclofenac: Effect on the Signs and Symptoms of Osteoarthritis") could not be located.

### Conclusions

A 45-day planning/filing meeting is scheduled for January 30, 1996. From an administrative standpoint, the application is acceptable for filing. After filing, the sponsor plans to submit a CANDAs with the ability to resort and tabulate case report tabulations. The review team will discuss the need for case report tabulations on a per-patient basis at the team meeting. English translations of the case report forms, a revised table of clinical studies, and investigator CVs for #298 can be requested along with any other information identified by the respective reviewers.

**/S/**

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Consumer Safety Officer

**APPEARS THIS WAY  
ON ORIGINAL**

cc:

Original  
HFD-180/Div. Files  
HFD-180/BStrongin  
HFD-180/SFredd

*2/1/96  
Concur  
/S/*

draft: BS/January 25, 1996/c:\wpfiles\n\20607601.0  
r/d Initials: K.Johnson/January 30, 1996  
              B.Strongin/January 31, 1996  
final: BS/January 31, 1996

CSO REVIEW

**APPEARS THIS WAY  
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0001. Expiration Date: December 31, 1995. See OMB Statement on Page 3.	
<b>APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE          OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, 314)</i>		<b>FOR FDA USE ONLY</b>	
		DATE RECEIVED	DATE FILED
		DIVISION ASSIGNED	NDA/ANDA NO. ASS.
NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).			
NAME OF APPLICANT		DATE OF SUBMISSION	
G.D. Searle & Co.		6-17-97	
ADDRESS (Number, Street, City, State and ZIP Code)		TELEPHONE NO. (Include Area Code)	
4901 Searle Parkway Skokie, IL 60077		(874) 982-8606	
		NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)	
		20-607	
<b>DRUG PRODUCT</b>			
ESTABLISHED NAME (e.g., USP/USAN)		PROPRIETARY NAME (If any)	
diclofenac sodium/misoprostol		Arthrotec®	
CODE NAME (If any)	CHEMICAL NAME 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, mono-sodium salt/(±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate		
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)	
Tablet	Oral	50mg/200mcg 75mg/200mcg	
PROPOSED INDICATIONS FOR USE			
reatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis			
LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:			
<b>INFORMATION ON APPLICATION</b>			
TYPE OF APPLICATION (Check one)			
<input checked="" type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)			
IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
NAME OF DRUG		HOLDER OF APPROVED APPLICATION	
TYPE SUBMISSION (Check one)			
<input type="checkbox"/> PRE SUBMISSION <input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> SUPPLEMENTAL APPLICATION			
<input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> RESUBMISSION			
SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____			
PROPOSED MARKETING STATUS (Check one)			
<input checked="" type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) <input type="checkbox"/> APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)			

AMENDED PATENT STATEMENT UNDER 21 USC 355(b)(1)

Drug Product (Drug) Patent

The previously identified U. S. patent 3,965,143 has now expired. There is no U. S. Patent now in existence directed to the drug misoprostol nor the drug diclofenac sodium contained in the fixed combination product which is the subject of the present application:

Drug Product (Formulation) Patents

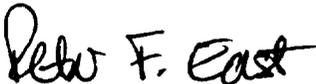
The following U. S. Patents contain claims directed to formulations/dosage forms of the active agent misoprostol or the active agent misoprostol in combination with the active agent diclofenac sodium in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

<u>Patent Number</u>	<u>Owner</u>	<u>Title</u>	<u>Expiration</u>
4,301,146	G. D. Searle & Co.	Stabilization of 16-Oxygenated Prostanoic Acid Derivatives	July 29, 2000
5,601,843	G. D. Searle & Co.	Pharmaceutical Tablet Composition	February 11, 2014

The undersigned declares that the above patents cover formulations/dosage forms of the active agent misoprostol alone or in combination with the active agent diclofenac in the product which is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed U. S. Patents are assigned to G. D. Searle & Co., who is also the present NDA applicant.

  
\_\_\_\_\_  
Peter F. East  
Associate Director

**APPEARS THIS WAY  
ON ORIGINAL**

PATENT STATEMENT UNDER 21 USC 355(b)(1)Drug Product (Drug) Patent

The following U. S. Patent contains claims directed to the drug misoprostol which is contained in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

<u>Patent Number</u>	<u>Owner</u>	<u>Title</u>	<u>Expiration</u>
3,965,143	G. D. Searle & Co.	16-Oxygenated Prostanoic Acid Derivatives	Mar. 26, 1996

The undersigned declares that the above patent covers the active agent misoprostol in the product which is the subject of this application for which approval is being sought.

Drug Product (Formulation) Patents

The following U. S. Patent contains claims directed to formulations/dosage forms of the active agent misoprostol in the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application:

<u>Patent Number</u>	<u>Owner</u>	<u>Title</u>	<u>Expiration</u>
4,301,146	G. D. Searle & Co.	Stabilization of 16-Oxygenated Prostanoic Acid Derivatives	July 29, 2000

The undersigned declares that the above patent covers formulations/dosage forms of the active agent misoprostol in the product which is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed U. S. Patents are assigned to G. D. Searle & Co., who is also the present NDA applicant.

CLAIMED PRODUCT EXCLUSIVITY Under 21 USC 355 D(iii)

The present applicant, G. D. Searle & Co. is claiming exclusivity under 21 CFR §314.108(b)(4) for the diclofenac sodium/misoprostol fixed combination product which is the subject of the present application.

New Clinical Investigations:

The undersigned certifies that to the best of applicant's knowledge that each of the clinical investigations included in the present application meets the definition of "new clinical investigation" set forth in §314.108(a).

Essential to Approval:

The undersigned certifies that the applicant has thoroughly searched the scientific literature and, to the best of applicant's knowledge, there are no published studies or publically available reports of clinical investigation regarding the indications of acute and chronic treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis for a combination drug product containing the active ingredients misoprostol and diclofenac sodium in a fixed combination. The clinical studies contained in this application were determined to be essential to approval of the diclofenac sodium/misoprostol fixed combination tablet.

Conducted or Sponsored by:

The undersigned certifies that the applicant was the sponsor named in the Form FDA-1571 for an investigational new drug application under which the new clinical investigations which are essential to approval were conducted.

APPEARS THIS WAY  
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-607 SUPPL # \_\_\_\_\_

Trade Name Arthrotec Tablets  
Generic Name diclofenac sodium/misoprostol  
Applicant Name G.D. Searle & Company HFD- 180

Approval Date December 19, 1997

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?  
YES / X / NO / \_\_\_ /

b) Is it an effectiveness supplement?  
YES / \_\_\_ / NO / X /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / \_\_\_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?  
YES / \_\_\_ / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

\_\_\_\_\_

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-201 Voltaren (diclofenac sodium) Tablets

NDA # 19-268 Cytotec (misoprostol) Tablets