

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

Subject	Treatment	Cmax	Tmax	AUC0-12	AUCinf	AUClast	AUC0-4
18, 8/22/97	A,D	1390	2.55	2567.92	2514.18	2480.04	n/a
18, 9/10/97	A,D	1390	2.55	2585.33	2586.09	2480.04	n/a
26 8/22/97	A,M	465	0.5	n/a	684.19	468.79	468.79
26 9/10/97	A,M	465	0.5	n/a	680.75	468.79	468.79
30 8/22/97	C	1270	0.17	n/a	594.23	586.33	612.79
30 9/10/97	C	1270	0.17	n/a	594.23	586.33	612.79
28 8/22/97	V	2040	0	3563.68	3582.35	3522.28	
28 9/10/97	V	1960	2.05	3563.68	3582.35	3522.28	

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

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

APPEARS THIS WAY
ON ORIGINAL

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

Statistical Analysis of diclofenac pharmacokinetic data Study 359:

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

APPEARS THIS WAY
ON ORIGINAL

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV)		Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
	Test	Reference			
MISOPROSTOL ACID COMPONENT					
Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	438.50(34)	492.70(44)	0.90	0.84,0.96	Pass
AUCinf (pg.hr/mL)	475.75 (37)	528.02 (43)	0.90	0.83,0.98	Pass
Cmax (pg/mL)	677.31 (62)	823.95 (60)	0.81	0.71,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	438.50(34)	442.29(37)	0.99	0.92,1.06	Pass
AUCinf (pg.hr/mL)	475.75 (37)	459.18 (37)	1.00	0.92,1.08	Pass
Cmax (pg/mL)	677.31 (62)	725.92 (58)	0.89	0.79,1.01	Fail
Voltaren given with Cytotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	442.29(37)	492.70(44))	91	0.85,0.97	Pass
AUCinf (pg.hr/mL)	459.18 (37)	528.02(43)	0.90	0.84,0.96	Pass
Cmax (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.83,0.97	Pass

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

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

CONCLUSIONS:

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

Protocol NN2-97-02-360

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

OBJECTIVE

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

Demographics:

38 male, 14 female subjects

Mean age = 27 yr

Mean B.Wt. = 71.8 Kg

METHODS:

Study Design:

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

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

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

Subjects:

Fifty-two subjects took part in the study.

Treatment and Administration:

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

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

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

Formulations/Clinical Supplies:

- ▶ tablets containing an enteric-coated core of
diclofenac sodium 50 mg with an containing misoprostol 200 mcg

Batch No. 787900

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

Pharmacokinetic Analysis:

T_{max}, t_{lag}, C_{max}, C_{min}, AUC_{0-lqc} and AUC_{0-inf}, AUC_{0-12hr}(diclofenac) and AUC_{0-inf} and AUC_{0-4hr}(misoprostol) were reported.

Analytical Methods:

RESULTS

Statistical Analysis of diclofenac pharmacokinetic data, Study 360:

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

Statistical Analysis of misoprostol acid pharmacokinetic data Study 360:

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

CONCLUSIONS

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

Dissolution Update:

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

Diclofenac Sodium:

Misoprostol:

FDA response: The following dissolution method is acceptable in light of the sponsor's

This was discussed and agreed upon with the Chemistry Reviewer.

Study 359 - Arthrotec 75 mg														
DICLOFENAC														
Study 359 Arthrotec vs. Voltaren														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
AUC12	7.715478	7.528058	-0.18742	-0.25827	-0.11657	2242.794	1859.491	0.829096	0.7723878	0.88997	0.042644	51	93	
AUCL	7.694534	7.510471	-0.18406	-0.25491	-0.11322	2196.31	1827.074	0.831883	0.7749892	0.89295	0.0426406	51	93	
CMAx	7.627758	7.287447	-0.34031	-0.45767	-0.22295	2054.439	1461.834	0.711549	0.6327538	0.80016	0.0706409	51	93	
Study 359 Arthrotec vs. Combo														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
AUC12	7.635245	7.528058	-0.10719	-0.17895	-0.03542	2069.877	1859.491	0.898358	0.8361471	0.9652	0.0431948	51	93	
AUCL	7.615912	7.510471	-0.10544	-0.1772	-0.03368	2030.245	1827.074	0.899928	0.8376087	0.96688	0.0431944	51	93	
CMAx	7.566253	7.287447	-0.27881	-0.39769	-0.15993	1931.888	1461.834	0.756687	0.6718738	0.85221	0.0716534	51	93	
Study 359 Combo vs. Voltaren														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
AUC12	7.715478	7.635245	-0.08023	-0.15269	-0.00778	2242.794	2242.794	0.922901	0.8583958	0.99225	0.0436256	51	96	
AUCL	7.694534	7.615912	-0.07862	-0.15107	-0.00617	2196.31	2030.245	0.924389	0.8597847	0.99385	0.0436221	51	96	
CMAx	7.627758	7.566253	-0.06151	-0.18153	0.058522	2054.439	1931.888	0.940348	0.8339915	1.06027	0.072267	51	96	
MISOPROSTOL														
Study 359 Arthrotec vs. Cytotec														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval			reference	test		Interval				
AUC4	6.122448	6.01605	-0.1064	-0.17197	-0.04083	455.9794	409.9581	0.899067	0.842008	0.95999	0.0394779	51	96	
AUCL	6.073294	5.961415	-0.11188	-0.18268	-0.04108	434.1083	388.1592	0.894153	0.8330361	0.95975	0.0426278	51	96	
CMAx	6.553249	6.337804	-0.21545	-0.33637	-0.09452	701.5199	565.5531	0.806183	0.7143586	0.90981	0.0728078	51	96	

Study 359 Arthrotec vs. Combo													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
JCA	6.028676	6.01605	-0.01283	-0.07861	0.053383	415.1649	409.9581	0.987454	0.9243968	1.05481	0.0397309	51	96
JCL	6.965989	6.961415	-0.00457	-0.07583	0.06668	389.9384	388.1592	0.995437	0.9269768	1.06895	0.042901	51	96
MAX	6.453404	6.337804	-0.1156	-0.2373	0.0061	634.8598	565.5531	0.890832	0.7887545	1.00612	0.0732744	51	96
Study 359 Combo vs. Cytotec													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
JCA	6.028676	6.122448	0.093772	0.027783	0.15978	415.1649	415.1649	1.098309	1.0281731	1.17323	0.0397309	51	96
JCL	6.073294	6.965989	-0.10731	-0.17858	-0.03605	434.1083	389.9384	0.898251	0.836475	0.98459	0.042901	51	96
MAX	6.553249	6.453404	-0.09985	-0.22155	0.021855	701.5199	634.8598	0.904978	0.8012796	1.0221	0.0732744	51	96
Study 360 - Arthrotec 50 mg													
Study 360 Arthrotec vs. Voltaren													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
IC12	7.14592	7.031967	-0.11395	-0.2091	-0.0188	1268.918	1132.258	0.8923	0.8113135	0.98137	0.0572155	47	85
JCL	7.117644	7.009005	-0.10864	-0.20881	-0.01088	1233.541	1106.553	0.897054	0.8133331	0.98939	0.0589158	47	85
MAX	7.089433	6.762873	-0.32656	-0.47988	-0.17324	1199.227	865.1245	0.721402	0.6188592	0.84094	0.092195	47	85
Study 360 Arthrotec vs. Combo													
	ls mean (log)		difference	90% Confidence		geometric mean		geometric mean ratio	90% Confidence		std error (difference)	n	df (MSE)
	reference	test		Interval		reference	test		Interval				
IC12	6.99547	7.031967	0.036497	-0.05952	0.132513	1091.676	1132.258	1.037172	0.9422181	1.14169	0.0577373	47	85
JCL	6.962336	7.009005	0.046669	-0.0522	0.145539	1056.098	1106.553	1.047778	0.9491392	1.15868	0.0594531	47	85
MAX	6.936692	6.762873	-0.17382	-0.32853	-0.0191	1029.359	865.1245	0.84045	0.7198779	0.98108	0.0930359	47	85

Study 360 Combo vs. Voltaren														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test	mean ratio	Interval		(difference)		
IC12	7.14592	6.99547	-0.15045	-0.24583	-0.05527		1268.918	1091.676	0.860321	0.7822114	0.94623	0.0572347	47	85
ICL	7.117644	6.962336	-0.15531	-0.25332	-0.0573		1233.541	1056.098	0.856151	0.7762219	0.94431	0.0589355	47	85
MAX	7.089433	6.936692	-0.15274	-0.30597	0.000483		1199.227	1029.359	0.858352	0.7364119	1.00048	0.0922259	47	93
MISOPROSTOL														
Study 360 Arthrotec vs. Cytotec														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test	mean ratio	Interval		(difference)		
IC4	6.061401	5.949839	-0.11158	-0.16957	-0.05355		428.9759	383.6915	0.894438	0.8440281	0.94785	0.0348906	47	87
ICL	5.974725	5.852956	-0.12177	-0.19081	-0.05273		393.3598	348.2623	0.885353	0.8262891	0.94864	0.0415275	47	87
MAX	6.519337	6.346648	-0.17269	-0.24805	-0.09733		678.1289	570.5768	0.841399	0.7803194	0.90726	0.0453292	47	87
Study 360 Arthrotec vs. Combo														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test	mean ratio	Interval		(difference)		
IC4	5.989754	5.949839	-0.03991	-0.09743	0.017596		399.3162	383.6915	0.960871	0.9071699	1.01775	0.0345918	47	87
ICL	5.918932	5.852956	-0.06598	-0.13443	0.002474		372.0142	348.2623	0.936153	0.874217	1.00248	0.0411719	47	87
MAX	6.387441	6.346648	-0.04079	-0.11551	0.033924		594.3334	570.5768	0.960028	0.890912	1.03451	0.044941	47	87
Study 360 Combo vs. Cytotec														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test	mean ratio	Interval		(difference)		
IC4	6.061401	5.989754	-0.07165	-0.12919	-0.0141		428.9759	428.9759	0.930859	0.8788068	0.988	0.0346114	47	87
ICL	5.974725	5.918932	-0.05579	-0.12428	0.012897		393.3598	372.0142	0.945735	0.8831308	1.01278	0.0411952	47	87
MAX	6.519337	6.387441	-0.1319	-0.20668	-0.05714		678.1289	594.3334	0.876431	0.8132992	0.94448	0.0449665	47	87

Updated 9/11

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

Study 359 Arthrotec vs. Combo														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test		mean rati	Interval			
UC4	6.028685	6.016611	-0.01207	-0.07814	0.053994	415.1689	410.1861	0.987998	0.9248327	1.05548	0.0397789	51	96	
UCInf	6.08179	6.077802	-0.00399	-0.08618	0.078208	437.8122	436.0698	0.99602	0.917425	1.08135	0.0494575	51	90	
MAX	6.453404	6.337804	-0.1156	-0.2373	0.0061	634.8598	565.5531	0.890832	0.7887545	1.00612	0.0732744	51	96	
Study 359 Combo vs. Cytotec														
	ls mean (log)		difference	90% Confidence			geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval			reference	test		mean rati	Interval			
UC4	6.122424	6.028685	-0.09374	-0.15981	-0.02767	455.9687	455.9687	0.910521	0.8523083	0.97271	0.0397789	51	96	
UCInf	6.185707	6.08179	-0.10392	-0.18708	-0.02076	485.7562	437.8122	0.9013	0.8293788	0.97946	0.0500382	51	90	
MAX	6.553249	6.453404	-0.09985	-0.22155	0.021855	701.5199	634.8598	0.904978	0.8012796	1.0221	0.0732744	51	96	

**APPEARS THIS WAY
ON ORIGINAL**

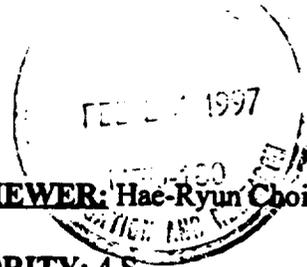
FEB 24 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-607

SUBMISSION DATE: 12/20/96

Arthrotec® (diclofenac sodium/misoprostol) Tablets
50 mg/200 mcg & 75 mg/200 mcg
G.D. Searle & Company
Skokie, IL 60077



REVIEWER: Hae-Ryun Choi, Ph.D.

TYPE OF SUBMISSION: NDA Amendment

PRIORITY: 4 S

SYNOPSIS:

The firm has submitted the current amendment in response to the Biopharmaceutics Comments sent by the Division of Pharmaceutical Evaluation II on 11/22/96. The comment is written in Bold followed by the review of the sponsor's response.

1. Please provide data from studies which directly compare the proposed market image of Arthrotec to marketed Voltaren and Cytotec to demonstrate that in the Arthrotec market image and misoprostol in the Arthrotec market images are bioequivalent to Voltaren and Cytotec.

In this amendment, the firm has provided the same data from studies (-332, -354, -346, -347, and -353), which were originally submitted in Arthrotec NDA 20-607, to address the bioequivalence issues. The following are the conclusions regarding the bioequivalence based on the data submitted.

a. Arthrotec 50:

Diclofenac Component: Bioequivalency has been demonstrated between diclofenac contained in Arthrotec clinical supply I and Voltaren 50 mg tablet alone for diclofenac $AUC_{(0-\infty)}$ and C_{max} . Arthrotec except for the method of misoprostol and site(s) of manufacture, was the same formulation as Arthrotec market image by study -354. The diclofenac in the Arthrotec market image was shown to be bioequivalent to diclofenac in Arthrotec in terms of diclofenac $AUC_{(0-\infty)}$ and C_{max} .

Misoprostol Component: Bioequivalency has been demonstrated between misoprostol in Arthrotec and the marketed Cytotec alone for misoprostol acid $AUC_{(0-1qc)}$ and C_{max} . Arthrotec, except for the method of misoprostol synthesis (duplex vs. simplex) and site(s) of manufacture, was the same formulation as the Arthrotec, which was linked to the Arthrotec market image by study

-354. Bioequivalency has been demonstrated between misoprostol in the Arthrotec market image and misoprostol in Arthrotec for misoprostol acid $AUC_{(0-\infty)}$, but not for misoprostol acid C_{max} (C_{max} ratio for Arthrotec market image Arthrotec = 87.8%, 90% C.I. = 75.2%, 102.6%).

b. Arthrotec 75:

Diclofenac Component: In multiple-dose study -347, bioequivalency has been demonstrated between diclofenac in Arthrotec and the marketed Voltaren 75 mg tablet alone for diclofenac steady-state $AUC_{(0-12)}$, but not for diclofenac C_{max} (C_{max} ratio for Arthrotec clinical supply III/Voltaren = 86.5%, 90% C.I. = 71.9%, 103.9%). Note that BE studies are usually conducted as single dose studies and not multiple-dose (steady-state) studies. In comparison, single-dose study -346 submitted in original Arthrotec NDA 20-607 has demonstrated bioequivalency between those two formulations for diclofenac AUC , but not for diclofenac C_{max} (C_{max} ratio for Arthrotec Voltaren = 73.4%, 90% C.I. = 58.5%, 92.1%). Market image Arthrotec 75 and were shown to be bioequivalent each other in terms of diclofenac $AUC_{(0-\infty)}$ and C_{max} .

Misoprostol Component: Bioequivalency has been demonstrated between misoprostol in Arthrotec and marketed Cytotec for misoprostol acid AUC , but not for misoprostol acid C_{max} (C_{max} ratio for Arthrotec Cytotec = 106.8%, 90% C.I. = 90.0%, 126.8%) in single-dose study -346. Market image Arthrotec 75 and were shown to be bioequivalent each other in terms of misoprostol acid $AUC_{(0-\infty)}$ and C_{max} .

2. Please provide information to determine whether changes in the misoprostol daily dose interval (e.g. BID versus QID) for the same total daily dose affects the efficacy and safety of that component of Arthrotec.

Dr. Robie-Suh will go over the firm's response to this comment.

3. 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 attributed to age or gender. For misoprostol there was 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. We request a gender analysis including body weight as a covariate.

The firm has indicated that with misoprostol acid, there were no significant differences in weight normalized clearance attributable to gender or age. With diclofenac, there was no significant difference in weight normalized clearance attributable to age. No significant gender effect on weight normalized clearance (lq_c) was also noted, in contrast, a significant gender effect was

noted on weight normalized clearances(inf). However, these differences are not thought to be clinically important requiring dosage adjustments.

The firm's response to the above comment is acceptable.

4. Concerning Study 332:

There is a discrepancy between AUC values in your report and those calculated by the Agency for both diclofenac and misoprostol acid, although the 90% confidence intervals for diclofenac in your calculations and ours are similar. Please recheck the AUC data, and submit the results to us.

Also, your data showed that the mean AUC(0-4) and Cmax values for misoprostol acid from ARTHROTEC 50 (clinical supply I, study -332) were 235 (CV, 41%) pg.hr/ml and 441 (31%) pg/ml, respectively. Those from ARTHROTEC 75 (clinical supply III, 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. Comparing these parameters, the bioavailability of misoprostol acid from ARTHROTEC 50 (clinical supply I, 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

Please explain the relatively high misoprostol acid plasma levels seen in study -332.

Discrepancy between AUC values in -332 report.

It was found that the discrepancy between Agency and sponsor's AUC values in report -332 was due to the difference in the handling the plasma concentration values below detection limit. The firm's reported AUC values were calculated in a way that values below the detection limit (both in the absorption and elimination phases of the concentration-time curve) were excluded in the AUC determinations. The firm has submitted the recalculated AUCs by different methods in this amendment. The Agency's AUC values were similar to the firm's recalculated AUC values, where the values below the detection limit in the elimination phase only were excluded in the AUC determinations.

The firm's response to the above comment is acceptable.

Please explain the relatively high misoprostol acid plasma levels seen in study -332.

It is indicated that since bio-studies -332 and -346 demonstrated that both misoprostol acid AUC for the Arthrotec 50 and Arthrotec 75 were bioequivalent to marketed Cytotec, it is concluded that cross comparison of misoprostol acid AUC values from study -332 and study -346 does not imply greater bioavailability.

The firm's response to the above comment is acceptable.

5. For the assessment of bioequivalence, you used SAS PROC GLM containing terms for sequence, subject (nested within sequence), period, first order carryover and treatment as factors. The Agency 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 C_{max} and (89.6%, 107.8%) for AUC(0-l_{qc}). In the statistical analyses, subjects # 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). Please consider the validity and impact of this reanalysis on conclusions regarding the bioequivalence of Arthrotec 50 tablets with diclofenac cores manufactured at different sites.

PROC MIXED vs. PROC GLM.

The firm's recalculated 90% confidence intervals for diclofenac AUC(0-l_{qc}) and C_{max} using PROC MIXED procedure were the same as Agency's. Both PROC MIXED and PROC GLM procedures lead to the same conclusions regarding the bioequivalence of the Secifarma diclofenac core in the proposed product and Arthrotec; equivalence was demonstrated for diclofenac AUC, but not for diclofenac C_{max}.

The firm's response to the above comment is acceptable.

Importance of study -345 in NDA 20-607.

The firm has indicated that study -345 is not pivotal concerning the bioequivalence of the proposed _____ and _____ Arthrotec. Study -354 is pivotal.

The firm's response to the above comment is acceptable.

6. The firm provided AUC(0-∞) values for diclofenac from only 20 subjects. This reviewer recalculated AUC(0-∞); for Canadian, proposed _____ and proposed _____ 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 _____ to _____ Arthrotec, this reviewer obtained the 90 % C.I. for diclofenac Cmax with 90% C.I.=73.9-107.9%; bioequivalency was not established.

ANOVA model with and without first order carryover.

The firm's recalculated 90 % C.I. for Cmax using an ANOVA model excluding first order carryover effects was (74.1%, 107.7%), which was similar to Agency's C.I. of (73.9%, 107.9%). The analysis using an ANOVA model with or without first order carryover lead to same conclusion; equivalency was not demonstrated for diclofenac Cmax between Secifarma diclofenac in _____

The firm's response to the above comment is acceptable.

7. We suggest the following dissolution conditions and specifications for Arthrotec:

Diclofenac

Misoprostol

The firm has stated that a response to this request will be included in CMC amendment later.

RECOMMENDATIONS:

The Division of Pharmaceutical Evaluation II has reviewed an amendment to Arthrotec NDA 20-607 and found acceptable.

The Medical Officer(s) is requested to consider the following:

1. **Concerning Arthrotec 50:**

diclofenac contained in the Arthrotec 50 market image was shown to be bioequivalent to the marketed Voltaren 50 mg tablet alone in terms of diclofenac AUC and C_{max} . Note that this was an indirect link.

Misoprostol in the Arthrotec 50 market image was shown to be bioequivalent to the marketed Cytotec alone for misoprostol acid AUC, but not for misoprostol acid C_{max} . Note that this was an indirect link.

2. **Concerning Arthrotec 75:**

diclofenac in the market image Arthrotec 75 was shown to be bioequivalent to the marketed Voltaren 75 mg tablet alone for diclofenac AUC, but not for diclofenac C_{max} after single or multiple-dosing.

Misoprostol in the market image Arthrotec 75 was shown to be bioequivalent to the marketed Cytotec alone for misoprostol acid AUC, but not for misoprostol acid C_{max} .

/S/

02/24/97

Hae-Ryun Choi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

APPEARS THIS WAY
ON ORIGINAL

RD/FT initialed by Lydia Kaus, Ph.D., Team Leader /S/ 2/24/97

cc: NDA 20-607 (BB, BL), HFD-180, HFD-870 (ML.Chen, Hunt, Kaus, Choi), HFD-850 (Millison), HFD-340 (Viswanathan).

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: November 7, 1996

FROM: Hae-Ryun Choi, Ph.D., Reviewer
Division of Pharmaceutical Evaluation II, HFD-870
Office of Clinical Pharmacology and Biopharmaceutics

TO: Drug Files of NDA 20-607

THROUGH: Lydia Kaus, Ph.D., Team Leader
Division of Pharmaceutical Evaluation II, HFD-870

LUK 11/8/96

SUBJECT: Arthrotec (diclofenac sodium/misoprostol)



This memo is in response to the Dr. Fredd's questions re Arthrotec bio data (E-mail dated 11/07/96).

Each question is written in Bold followed by the response.

1) IS SEARLE'S DICLOFENAC BIOEQUIVALENT TO CIBA'S DICLOFENAC?

A. 50 mg Strength

Secifarma Diclofenac/placebo	vs.	Ciba-Geigy Diclofenac
AUC	=	AUC
Cmax	=	Cmax

Secifarma diclofenac/placebo is BE to Ciba-Geigy diclofenac.

B. 75 mg Strength

Diclofenac/placebo was not compared to Ciba-Geigy diclofenac.

Note that Generics have separate BE study for each strength. NDA's will waive lower strength, if higher strength has BE study and lower strength is compositionally proportional and linear kinetics are shown over the dose range. The approved labeling for Voltaren states, "The area-under-the plasma-concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose proportional and are approximately 1.5 and 2.0 mcg/ml for 50 mg and 75 mg doses, respectively."

2) IS SEARLE'S DICLOFENAC IN THE COMBO TO BE MARKETED WITH MISOPROSTOL BIOEQUIVALENT TO SEARLE'S DICLOFENAC WITH THE PLACEBO MISOPROSTOL?

A. 50 mg Strength

Diclofenac/placebo	vs.	Ciba-Geigy Diclofenac	vs.	Combo	
AUC	=	AUC	=	AUC	
Cmax	=	Cmax	=	Cmax	
Combo	vs.		vs.	Combo	vs. Combo
Diclofenac				Diclofenac	Diclofenac
					To be marketed)
No study		AUC	=	AUC	= AUC
No study		Cmax	>	Cmax	< Cmax
		[ratio (A	= 97.5%	[ratio (B/A)=102.9%	
		90% C.I. = 74.0%, 107.9%]		90% C.I. = 83.4%, 127.0%]	
			vs.		
		AUC	=	AUC	
		Cmax	=	Cmax	

Conclusion:

- a. diclofenac/placebo is BE to Ciba-Geigy diclofenac.
- b. Combo diclofenac (to be marketed) was not compared directly to diclofenac/placebo.
- c. Combo diclofenac was not compared to However, the firm stated that are nearly identical in formulation. The differences being in the misoprostol and site(s) of manufacture.

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ON ORIGINAL**

B. 75 mg Strength

Combo vs. Combo vs. Ciba-Geigy
Diclofenac Diclofenac Diclofenac
(To be marketed)

AUC = AUC = AUC
Cmax = Cmax << Cmax
[ratio (Ciba) = 73.4%,
90% C.I. = 58.5%, 92.1%]

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ON ORIGINAL

Conclusion:

- a. Diclofenac/placebo was not compared to Ciba-Geigy diclofenac.
- b. diclofenac was not BE to Ciba-Geigy diclofenac.

3) IN THE FOOD EFFECTS STUDY OF SEARLE'S DICLOFENAC VERSUS CIBA'S DICLOFENAC, DO THOSE FINDINGS CHANGE YOUR RESPONSE TO 1 OR 2 ABOVE?

A. 50 mg Strength

Searle vs. Ciba-Geigy
Diclofenac/placebo Diclofenac

AUC = AUC
Cmax < Cmax
[Ratio (Searle/Ciba) = 89.4%,
90% C.I. = 66.2%, 120.5%]

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In a single dose study, under fed conditions, Searle diclofenac/placebo was not BE to Ciba-Geigy diclofenac.

B. 75 mg Strength

- a. No single dose study with 75 mg strength comparing Searle diclofenac/placebo and Ciba-Geigy diclofenac.
- b. Combo food study was a multiple dose study so comparison to single dose is difficult.

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ON ORIGINAL

4) IS MISOPROSTOL IN THE TO BE MARKETED COMBO TABLET BIOEQUIVALENT TO SEARLE'S MARKETED CYTOTEC? IF NOT, WHAT ARE THE DIFFERENCES THAT FALL OUTSIDE THE ACCEPTABLE BIO RANGE?

A. 50 mg Strength

Combo Misoprostol	vs.	Cytotec alone	
AUC	=	AUC	
Cmax	=	Cmax	
Combo Misoprostol	vs.		vs. Combo Misoprostol
			Product B)
Not studied		AUC	= AUC
Not studied		Cmax	> Cmax
		[Ratio = 87.8%, 90% C.I. = 75.2%, 102.6%]	

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Conclusion:

a. Cytotec was not compared directly to "to be marketed" Product

B. 75 mg Strength

Combo Misoprostol To be marketed	vs.	Misoprostol	vs.	Cytotec alone
AUC	=	AUC	=	AUC
Cmax	=	Cmax	>	Cmax
		[Ratio (Cytotec) = 106.8%, 90% C.I. = 90.0%, 126.8%]		

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Conclusion:

a. Misoprostol in the "to be marketed" Combo was not BE to marketed Cytotec.

APPEARS THIS WAY ON ORIGINAL

/S/

11/08/96

APPEARS THIS WAY
ON ORIGINAL

Hae-Ryun Choi, Ph.D
Division of Pharmaceutical Evaluation II

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

attachment: E-mail

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ON ORIGINAL

Handwritten signature

OCT 31 1996

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-607

SUBMISSION DATE:

12/22/95

02/23/96

Arthrotec[®] Tablets

05/09/96

diclofenac sodium/misoprostol, 50 mg/200 mcg & 75 mg/200 mcg

05/23/96

G.D. Searle & Co.

Skokie, IL 60077

REVIEWER: Hae-Ryun Choi, Ph.D.

TYPE OF SUBMISSION: Original NDA

PRIORITY: 4 S

SYNOPSIS

Arthrotec 50 vs. Combination Study: In an open-label study, each subject received single doses of the following four treatments in a randomized, crossover manner: a) one Voltaren 50 mg tablet; b) one Cytotec 200 mcg tablet; c) one Voltaren tablet plus one Cytotec tablet coadministered; and d) one Arthrotec 50 tablet (diclofenac 50mg/misoprostol 200 mcg, clinical supply I). Each dose was administered under fasted conditions. It was shown that Arthrotec 50 and Voltaren alone were bioequivalent with respect to diclofenac AUC and C_{max}; Arthrotec 50 and Cytotec alone were also bioequivalent with respect to misoprostol acid AUC and C_{max}. Arthrotec 50 was shown to be bioequivalent to Voltaren + Cytotec coadministration with respect to diclofenac AUC, misoprostol acid AUC and C_{max}. However, bioequivalency of the two treatments could not be demonstrated for diclofenac C_{max} (C_{max} ratio = 88.7%, 90% C.I. = 79.3%, 99.2%). Note that the link/BE study was between _____ and final market formulations.

Arthrotec 75 vs. Combination Study: In an open-label study, each subject received single doses of the following four treatments in a randomized, crossover manner: a) one Voltaren 75 mg tablet; b) one Cytotec 200 mcg tablet; c) one Voltaren tablet plus one Cytotec tablet coadministered; and d) one Arthrotec 75 tablet (diclofenac 75mg/misoprostol 200 mcg, clinical supply III). Each dose was administered under fasted conditions. It was shown that Arthrotec 75 and Voltaren alone were bioequivalent with respect to diclofenac AUC; Arthrotec 75 and Cytotec alone were also shown to be bioequivalent with respect to misoprostol acid AUC. Mean diclofenac C_{max} for Arthrotec 75 was significantly lower than that for Voltaren alone; bioequivalency of the two treatments could not be demonstrated for the rate of diclofenac absorption in terms of C_{max} (C_{max} ratio = 73.4%, 90% C.I. = 58.5%, 92.1%). Mean misoprostol acid C_{max} for Arthrotec 75 was not significantly different from that for Cytotec alone, however, bioequivalency of the two treatments could not be demonstrated for the rate of misoprostol acid absorption in terms of C_{max} (C_{max} ratio = 106.8%, 90% C.I. = 90.0%, 126.8%). Bioequivalency of Arthrotec 75 and Voltaren + Cytotec coadministration could not be demonstrated for either diclofenac or misoprostol acid AUC and C_{max}; diclofenac AUC ratio = 108.6%, 90% C.I. = 93.6 - 125.9%, diclofenac C_{max} ratio = 75.9%, 90% C.I. = 60.5 - 95.2%, misoprostol acid AUC ratio = 112.8%, 90% C.I. = 101.5 - 125.4%, and misoprostol acid C_{max} ratio = 113.4%, 90% C.I. = 95.5 - 134.6%, respectively.

Pivotal/Link Bioequivalence Studies for Arthrotec 50: The U.S. proposed Arthrotec 50 tablets A and B differ only in the source of diclofenac. The source for [redacted] while [redacted] for [redacted]. With the Arthrotec 50 tablets, there is no direct link between the proposed [redacted] and the [redacted]. Instead, the proposed [redacted] were indirectly linked to the [redacted] via the [redacted] Arthrotec tablets, which were nearly identical in formulation to [redacted]. The differences being in the misoprostol [redacted] and site(s) of manufacture [redacted] was the original formulation used in early clinical efficacy/safety trials. [redacted] was the formulation used in two pivotal U.S. clinical efficacy trials (NN2-95-06-349, NN2-95-06-352).

The aqueous diclofenac 50 mg/simplex misoprostol 200 mcg combination tablets [redacted] were bioequivalent to the reference organic diclofenac 50 mg/duplex misoprostol 200 mcg combination tablets [redacted] with respect to both diclofenac and misoprostol acid AUC and Cmax.

In comparison of [redacted] formulation, equivalence was established for the extent of diclofenac absorption in terms of AUC, however, not for the rate of diclofenac absorption in terms of Cmax (90% C.I. = 74.0%, 107.9%). Equivalence was also shown for misoprostol acid AUC and Cmax.

In comparison of [redacted] formulation, equivalence was shown for diclofenac AUC and Cmax. Equivalence was also shown for misoprostol acid AUC, but not for Cmax (Cmax ratio = 87.8%, 90% C.I. = 75.2%, 102.6%).

In comparison of [redacted] proposed product [redacted] equivalence was shown for the extent of diclofenac absorption, but not for the rate of absorption in terms of Cmax (Cmax ratio = 102.9%, 90% C.I. = 83.4%, 127.0%). Equivalence was also shown for the extent of misoprostol acid absorption, but not for the rate of absorption (Cmax ratio = 88.0%, 90% C.I. = 75.3%, 102.8%).

Bioequivalence Study for Arthrotec 75: With the Arthrotec 75 tablets, there is a direct bioavailability link between the proposed [redacted] used in pivotal U.S. clinical trials (NN2-95-06-349 and NN2-95-06-352). The Arthrotec 75 tablets used in the clinical trials were sourced from [redacted] chemical supplied [redacted]. The proposed [redacted] and contains diclofenac chemical supplied by [redacted]. It was shown that the tablets manufactured at [redacted] were bioequivalent to the tablets manufactured at [redacted] in terms of the rate and extent of diclofenac and misoprostol acid absorption.

Food Effect Studies: In a multiple-dose bioavailability study of Arthrotec 50 (clinical supply I), the morning doses on days 1 to 7 were given after fasted conditions; the final dose on day 8 was given after a high-fat meal. Compared to day 1, there was a statistically significant decrease in bioavailability of diclofenac (Cmax and AUC) and misoprostol acid (AUC) on day 7 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. Compared to fasted conditions, administration of Arthrotec 50 clinical formulation with a high-fat meal resulted in 68% decrease in diclofenac AUC (90% C.I. = 18.2%, 56.4%), 68% decrease in diclofenac C_{max} (90% C.I. = 17.6%, 60.0%), 24% increase in misoprostol acid AUC (90% C.I. = 112.4%, 137.6%), and 50% decrease in misoprostol acid C_{max} (90% C.I. = 41.6%, 59.9%), respectively; time to peak concentration (t_{max}) was increased for both components.

An open-label, randomized, crossover study with two multiple-dose treatments (Arthrotec 75 b.i.d. and Voltaren 75 mg b.i.d.) was conducted in healthy volunteers. The duration of each treatment was 6.5 days. The morning doses on the sixth and seventh days of each treatment were given under fasted and fed conditions. Under fasted conditions, the extent of diclofenac absorption from repeated twice daily doses of Arthrotec 75 (clinical supply III) was equivalent to that from marketed Voltaren 75 mg, however, not for the rate of absorption in terms of C_{max} (C_{max} ratio = 86.5%, 90% C.I. = 71.9%, 103.9%). Under fed conditions, mean diclofenac AUC and C_{max} values for Arthrotec 75 were higher than those for Voltaren given with food, respectively; AUC ratio = 137.4%, 90% C.I. = 96.3-196.2%, C_{max} ratio = 143.5%, 90% C.I. = 97.5-211.1%.

Food alters the multiple-dose bioavailability profile of Arthrotec 75. When Arthrotec 75 was taken with a high-fat meal, there was 20% decrease in diclofenac AUC (90% C.I. = 65.2%, 99.1%), 42% decrease in diclofenac C_{max} (90% C.I. = 46.7%, 72.2%), 6% increase in misoprostol acid AUC (90% C.I. = 97.2%, 115.5%), and 59% decrease in misoprostol acid C_{max} (90% C.I. = 34.9%, 48.6%), respectively, as compared to fasted conditions. T_{max} for both components was increased. There was no appreciable accumulation of either diclofenac or misoprostol acid in plasma following repeated doses of one Arthrotec 75 given every 12 hours under fasted conditions.

After single dose administration in elderly subjects, diclofenac mean AUC and C_{max} were decreased, when diclofenac 50 mg (Voltaren) was coadministered with misoprostol 200 mcg (Cytotec) as compared to diclofenac 50 mg 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 was no accumulation of diclofenac in plasma in fourth day of b.i.d. dosing with either diclofenac alone or diclofenac coadministered with misoprostol.

The extent of diclofenac absorption (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 [C_{max}(A.M.)] was 51% higher for Arthrotec 75 tablets than for Arthrotec 50 tablets.

The diclofenac 50 mg/placebo tablets, which were identical in appearance to Arthrotec but did not contain misoprostol in the outer mantle, were bioequivalent to the marketed Voltaren 50 mg tablets in terms of diclofenac AUC and C_{max} under fasted conditions.

The diclofenac chemical in diclofenac/placebo tablets supplied by [redacted] and the diclofenac chemical in diclofenac/placebo tablets used in previous clinical trials [redacted] 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 one outlier subject was excluded from the analysis.

The sponsor has adequately validated the assay methods for diclofenac and misoprostol acid.

RECOMMENDATION:

With the Arthrotec 50 tablets, there is no direct comparison between the proposed [redacted] compared to the [redacted] identical in formulation to [redacted] bioequivalent. However, the proposed [redacted] formulation in terms of diclofenac Cmax. The proposed [redacted] formulation in terms of misoprostol acid Cmax. Furthermore, the proposed [redacted] were not bioequivalent in terms of diclofenac and misoprostol acid Cmax.

No relationship has been established between plasma concentrations of misoprostol acid and therapeutic effect.

On the basis of Chemistry accepting proposed [redacted] and if the bioequivalence criteria of both rate and extent are essential for approval, then the sponsor might choose one of the following two options:

1. Clinical trial using to be marketed [redacted] in consultation with the Medical Division.
2. Bioequivalence study with following three arms: to be marketed [redacted] (formulation and manufacturing) with full new in date production lot, and marketed Cytotec.

With the Arthrotec 75 tablets, the proposed [redacted] was shown to be bioequivalent to the [redacted] used in the pivotal clinical trials.

The Medical Officer(s) should consider the above findings.

General Comments (pages 72-75) and Labeling Comments (pages 75-77) should be forwarded to the sponsor.

TABLE OF CONTENTS:

Page No.

Background	6
Bioequivalence of Arthrotec 50 vs. individual components as marketed tablets (Study -332)	15
Bioequivalence of Arthrotec 75 vs. individual components as marketed tablets (Study -346)	20
Bioequivalence of diclofenac/placebo and marketed Voltaren tablets (Study -316)	25
Bioequivalence of diclofenac/placebo and marketed Voltaren tablets (Study -342)	28
Bioequivalence of Arthrotec 50 clinical supplies (Study -343)	31
Bioequivalence of Arthrotec 50 clinical supplies (Study -345)	35
Bioequivalence of Arthrotec 50 clinical supplies (Study -354)	39
Bioequivalence of Arthrotec 75 clinical supplies (Study -353)	45
Drug interaction between diclofenac and misoprostol in elderly (Study -299)	50
Multiple-dose bioavailability and effect of food on Arthrotec 50 (Study -338)	54
Multiple-dose bioavailability and effect of food on Arthrotec 75 (Study -347)	57
Comparative bioavailability of Arthrotec 50 and Arthrotec 75 (Study -350)	62
Effect of age and gender	64
In-Vitro Dissolution	67
General Comments (to be sent to the firm)	72
Labeling Comments (to be sent to the firm)	75

APPENDIX:

Formulation Compositions	80
Biopharmaceutics Study Summary	81
In Vivo Analytical Methods Summary	82
Proposed Labeling	83
Figures	84
Individual In-Vitro Dissolution Data	85
Between- and Within-Subject Variability	86

BACKGROUND:

NDA 20-607 for Arthrotec (diclofenac sodium/misoprostol) Tablets was submitted by G.D. Searle & Co. on December 22, 1995. Arthrotec is a combination tablet containing diclofenac sodium, a nonsteroidal anti-inflammatory agent (NSAID), and misoprostol, a synthetic prostaglandin E₁ (PGE₁) analog with gastric antisecretory and mucosal protective properties. Arthrotec is proposed to be indicated for acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in patients at risk of developing NSAID-induced gastroduodenal ulcers. Two strengths of Arthrotec are available: Arthrotec 50 containing diclofenac sodium 50 mg and misoprostol 200 mcg and Arthrotec 75 containing diclofenac sodium 75 mg and misoprostol 200 mcg. The enteric-coated core containing diclofenac sodium, is surrounded by an outer mantle containing misoprostol. The proposed dosage of Arthrotec 50 for the treatment of OA is one tablet, two or three times per day, and that of Arthrotec 75 for the treatment of OA, is one tablet, two times per day. The proposed dosage of Arthrotec 50 for the treatment of RA is one tablet, two or three times per day, and that of Arthrotec 75 mg for the treatment of RA, is one tablet, two times per day.

Diclofenac sodium is currently marketed as Voltaren (Geigy), as 25, 50, and 75 mg enteric-coated tablets (NDA 19-201, approved on 7/28/88) for the treatment of OA and RA. The currently approved dose for diclofenac sodium in OA is 100-150 mg/day in two or three divided doses; that in RA is 100-200 mg/day, given in two, three or four divided doses. Doses above 200 mg/day in 3-4 divided doses have not been studied in RA patients.

Misoprostol is currently marketed as Cytotec (Searle) for the prevention of NSAID-induced gastric ulcers. When coadministered with therapeutic doses of NSAID for up to three months in patients with OA and RA, misoprostol 200 mg QID prevented the occurrence of NSAID-induced gastric and duodenal ulcers without interfering with the NSAID's antiinflammatory efficacy.

Guidance for generic diclofenac sodium tablets was issued by the Agency on 10/06/94. Types of studies required are: 1) a single-dose, randomized, fasting, two-period, two-treatment, two-sequence crossover study comparing equal doses of the test and reference products; 2) a single-dose, randomized, three-treatment, three-period, six-sequence crossover, limited food effect study comparing equal doses of the test and reference product when administered immediately following a standard breakfast.

The current approved labeling for Voltaren [diclofenac sodium delayed-release (enteric-coated tablets)] under PK section states, "Diclofenac sodium is completely absorbed from the gastrointestinal tract after fasting oral administration, with peak plasma levels occurring in 2-3 hours. However, due to first-pass metabolism, only 50% of the absorbed dose is systemically available. Peak plasma levels are achieved in 2 hours and the area-under-the plasma-concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose proportional and are approximately 1.5 and 2.0 mcg/ml for 50 mg and 75 mg doses, respectively. 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.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 ml/min and 550 mL/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin, and this has been shown not to be age dependent.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile.

Conjugates of unchanged diclofenac account for _____ of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted.

Conjugates of the principle metabolite account for _____ of the dose excreted in the urine and for _____ of the dose excreted in the bile.

Conjugates of three other metabolites together account for _____ of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life of these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. Some metabolites may have activity."

The current approved labeling for Cytotec under PK section states, "Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid, which is, thereafter, quickly eliminated with an elimination t_{1/2} of about 30 minutes. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose over the range of 200 to 400 mcg. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range. Neither the patient's age nor the concomitant administration of other highly protein-bound drugs affect the protein-binding of the drug.

Approximately 70% of the administered dose is excreted in the urine, mainly as biologically inactive metabolites. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of t_{1/2}, C_{max} and AUC compared to normals, but no clear correlation between the degree of impairment and the AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased without substantial changes in misoprostol elimination t_{1/2}.

Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme system in animals. In a study of subjects with hepatic impairment, 14 of 17 subject showed no correlation between the degree of hepatic impairment and misoprostol acid AUC or C_{max}. However, the three subject who had the lowest anti-pyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and C_{max} values.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food."

The firm's rationale for the development of combination tablet is as follows: 1) a single tablet provides the anti-arthritic properties of diclofenac and mucosal protectant properties of misoprostol; 2) absolutely ensures that the misoprostol and diclofenac are taken with each dose (i.e., compliance); 3) avoids the need for taking two medications; and 4) reduces the number of tablets that the patient must take daily.

During product development, a number of formulation changes have been made to the diclofenac and misoprostol components of Arthrotec.

The following table shows the different formulations used in various clinical trials.

Study No. (Indication) Protocol No.	Abbrev. Title	No of Sub	Clinical Supplies (I to III)
28 (OA) IN2-90-06-296 IN2-89-02-296	Efficacy and UGI Safety of Diclo/Miso in Osteoarthritis	361	Diclo 50-Miso 200 (I) Diclo 50-Placebo
29 (OA) IN2-90-06-298 IN2-89-02-298	Diclo/Miso in Treating Osteoarthritis	455	Diclo 50-Miso 200 (I) Diclo 50-Placebo (IV)
30 (OA) IN2-92-06-321 IN2-90-02-321	Diclo/Miso Comparative/Efficacy and UGI Safety in Osteoarthritis	643	Diclo 50-Miso 200 (I) Piroxicam 10 mg Naproxen 375 mg
31 (OA) NN2-95-06-349 NN2-94-02-349	Diclo/Miso Comparative/Efficacy and UGI safety vs Diclo in OA Osteoarthritis	572	Diclo 50-Miso 200 (II) Diclo 75-Miso 200 (III) Diclo 75-Placebo
32 (RA) IN2-90-06-289 IN2-89-02-289	Efficacy and UGI Safety of Diclo/Miso in Rheumatoid Arthritis	339	Diclo 50-Miso 200 (I) Diclo 50-Placebo
33 (RA) IN2-90-06-292 IN2-89-02-292	Diclo/Miso in Treating Rheumatoid Arthritis	346	Diclo 50-Miso 200 (I) Diclo 50-Placebo
34 (RA) NN2-95-06-352 NN2-94-02-352	Diclo/Miso Efficacy and Safety of Arthrotec I and II, Diclo and Placebo in RA	380	Diclo 50-Miso 200 (II) Diclo 75-Miso 200 (III) Diclo 75-Placebo

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The following table shows the lot number, date of manufacture, and expiry dates of these supplies.

Arthrotec Product	Manufacture Date	Expiry/Re-eval. Date	Drug Product Lot No.	Bioequivalence Protocol No.	Clinical Efficacy/Safety Protocol No.
	Nov 1988 Nov 1989		Multiple Lot No.		IN2-89-02-289 IN2-89-02-292 IN2-89-02-296 IN2-89-02-298
	Feb 1991	Jan 1992	P9101/034	NN2-91-02-343	EN2-89-02-304 IN2-90-02-321
	Sep 1991	May 1995	PT-135-91	NN2-91-02-343	NN2-94-02-349 NN2-94-02-351 NN2-94-02-352
	Aug 1993	Feb 1995	P9308/078	NN2-94-02-353	NN2-94-02-349 NN2-94-02-352
Proposed	Jul 1993 Sep 1994	Jul 1994 Sep 1995	480110 653310	NN2-93-02-345-01 NN2-95-02-354	
Proposed	Nov 1994	Nov 1995	664680	NN2-95-02-354	
Product	May 1993 Jul 1994	Mar 1995 Jul 1996	471740 639990	NN2-93-02-345-01 NN2-95-02-354	
Product	Sep 1994	Sep 1995	651060	NN2-94-02-353	

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In pivotal efficacy trials, fixed combination Arthrotec tablets were used, while in supportive studies, studies were performed using coadministration of diclofenac and misoprostol tablets. A placebo tablet with an

proposed enteric coating and the enteric coating.

The enteric coating formulation was used in these clinical studies:

IN2-89-02-289	IN2-89-02-292	EN2-88-02-293
IN2-89-02-296	IN2-89-02-297	IN2-89-02-298
EN2-89-02-302	NN2-89-02-303	EN2-90-02-304
IN2-90-02-305	EN2-91-02-306	IN2-89-01-310
NN2-89-02-316	IN2-90-02-321	NN2-90-02-329
NN2-91-02-332	NN2-91-02-338	NN2-91-02-342
NN2-91-02-343	NN2-93-02-345	NN2-95-02-354

The enteric coating formulation was used in these studies:

NN2-91-02-343	NN2-93-02-345	NN2-93-02-346
NN2-93-02-347	NN2-94-02-349	NN2-94-02-350

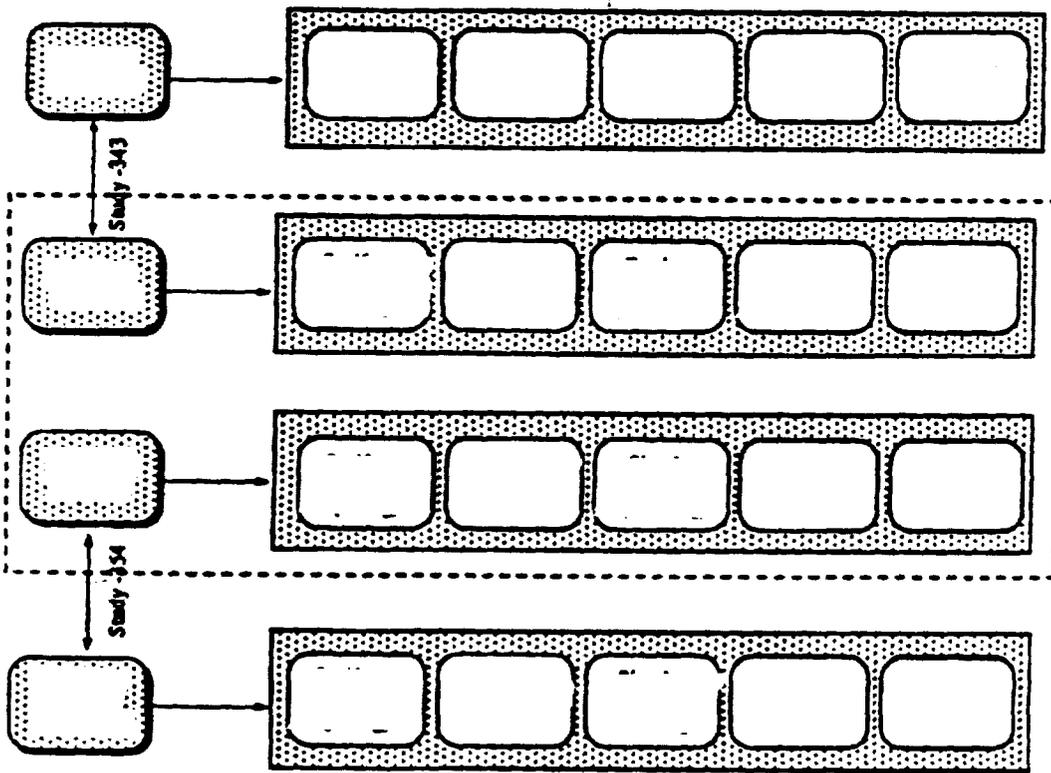
NN2-94-02-351
NN2-95-02-354

NN2-94-02-352

NN2-94-02-353

With the Arthrotec 50 tablets, there is no direct link between the proposed products
However, those were indirectly linked via the marketed Arthrotec
tablets which were identical to with the exception of misoprostol dispersion
and the site of manufacture. The firm has reported that at the time of conduction the
bioavailability evaluation (March 1995), the expiry date (Feb. 1991) had already passed for the
expiry date (May 1995) was very close. Clinical supply
I 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).

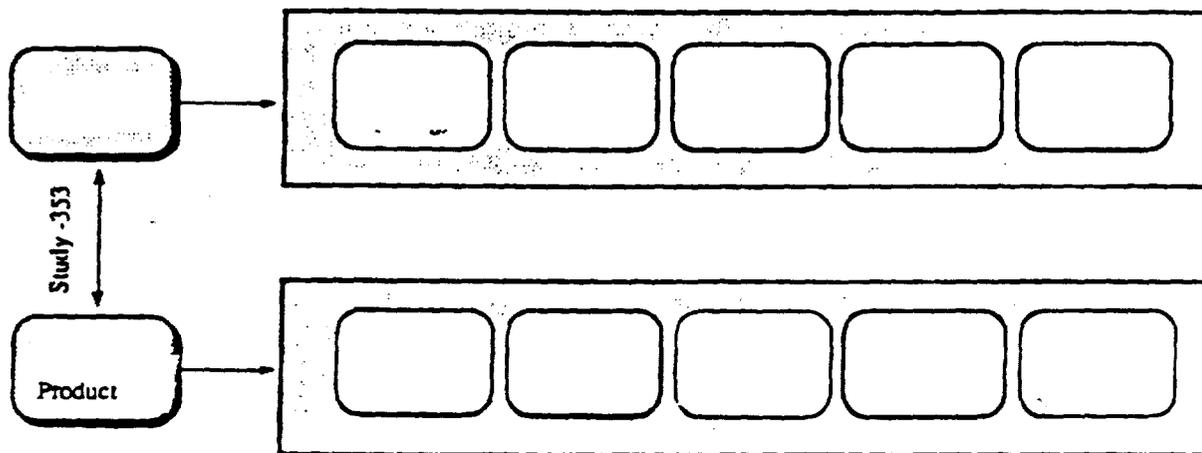
The following figure shows the bioequivalency link between and the proposed
marketed



With the Arthrotec 75 tablets, there is a direct bioavailability link between the
used in pivotal clinical trials and the proposed Clinical trials have been conducted
with diclofenac 75 mg/misoprostol 200 mcg tablets manufactured at

The proposed product will be manufactured at _____ In addition to the difference
in source of manufacture, _____ tablets contained diclofenac supplied by
while the _____ tablets contained diclofenac supplied by _____

The following figure shows the bioequivalency link between _____ used in the pivotal
clinical trials and the proposed _____



Bioequivalency should be determined on two active moieties, misoprostol and diclofenac. The analytical methods for both components have been validated. Plasma concentrations of both active moieties are very low; ng/mL range for diclofenac and pg/mL range for misoprostol acid.

Human pharmacokinetics and bioavailability section of this application contains 17 Bioavailability/bioequivalence studies which could be classified into the following:

1. Bioequivalence of Arthrotec 50 vs. individual components as marketed tablets
2. Bioequivalence of Arthrotec 75 vs. individual components as marketed tablets
3. Bioequivalence of diclofenac/placebo and marketed Voltaren tablets
4. Bioequivalence of Arthrotec 50 clinical supplies
5. Bioequivalence of Arthrotec 75 clinical supplies
6. Drug interaction between diclofenac and misoprostol in elderly
7. Multiple-dose bioavailability and effect of food on Arthrotec 50
8. Multiple-dose bioavailability and effect of food on Arthrotec 75
9. Comparative bioavailability of Arthrotec 50 and Arthrotec 75

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

<u>Study No</u>	<u>Title and Comment</u>
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. <u>Comment:</u> 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 <u>Comment:</u> 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 <u>Comment:</u> 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)

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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 (C_{max}), time to C_{max} (t_{max}), 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-l_{qc}) 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 C_{max} 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)	C _{max} (ng/mL)	t _{max} (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 C_{max}, AUC and t_{max} 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%)
	C _{max}	94.2%	(84.3 %, 105.3%)
Arthrotec 50/ Voltaren + Cytotec	AUC(0-∞)	112.7%	(106.0%, 119.9%)
	C _{max}	88.7%	<u>(79.3%, 99.2%)</u>
Voltaren + Cytotec/ Voltaren	AUC(0-∞)	92.1%	(86.6%, 97.9%)
	C _{max}	106.2%	(94.9%, 118.8%)

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

Treatment (N=36)	C _{max} (pg/mL)	t _{max} (hr)	AUC(0-l _{qc}) (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 C_{max}, AUC(0-l_{qc}) and t_{max} 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-l _{qc})	93.9%	(82.6%, 106.8%)
	C _{max}	96.4%	(85.3%, 109.0%)
Arthrotec 50/ Cytotec + Voltaren	AUC(0-l _{qc})	95.8%	(84.1%, 109.1%)
	C _{max}	97.2%	(85.9%, 110.0%)
Cytotec + Voltaren/ Cytotec	AUC(0-l _{qc})	98.0%	(86.0%, 111.6%)
	C _{max}	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-l_{qc}) 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-l_{qc}) 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, C_{max} occurred within 1 hour following appearance of drug in plasma.
5. The $AUC(0-l_{qc})$ for diclofenac contributed about 99% of $AUC(0-\infty)$. 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 C_{max} . However, the diclofenac C_{max} 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 C_{max} ; Arthrotec 50 mg is also bioequivalent to Cytotec alone for misoprostol acid AUC and C_{max} .
- Voltaren coadministered with Cytotec was bioequivalent to Voltaren alone for diclofenac AUC and C_{max} .
- Cytotec coadministered with Voltaren was bioequivalent to Cytotec alone for misoprostol acid AUC and C_{max} .

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) C_{max} , AUC and T_{max} 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 C_{max} , AUC and T_{max} 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 (C_{max}); time to C_{max} (t_{max}). 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-l_{qc}) 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)	C _{max} (ng/mL)	t _{max} (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)

**APPEARS THIS WAY
ON ORIGINAL**

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-l _q c)	102.7%	(86.0%, 122.6%)	0.805
	C _{max}	106.8%	(90.0%, 126.8%)	0.523
Arthrotec 75mg/ Cytotec + Voltaren	AUC(0-∞)	112.8%	(101.5%, 125.4%)	0.061
	AUC(0-l _q c)	125.9%	(105.4%, 150.4%)	0.034
	C _{max}	113.4%	(95.5%, 134.6%)	0.226
Cytotec + Voltaren/ Cytotec	AUC(0-∞)	86.7%	(78.0%, 96.4%)	0.028
	AUC(0-l _q c)	81.5%	(68.3%, 97.4%)	0.060
	C _{max}	94.2%	(79.4%, 111.8%)	0.564

Comments:

- This reviewer calculated AUC(0-∞) for diclofenac. It was found that AUC(0-l_qc) 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 C_{max} for Arthrotec 75 was significantly lower (p=0.026) than that for Voltaren alone; bioequivalency of the two treatments could not be demonstrated (C_{max} ratio = 73.4%, 90% CI = 58.5%, 92.1%). Mean misoprostol acid C_{max} 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 (C_{max} 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 C_{max}.

- Diclofenac coadministered with misoprostol was equivalent to diclofenac tablets given alone for AUC, but not for C_{max}; 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 C_{max}.

Sponsor's Labeling Claim: Diclofenac sodium C_{max}, AUC and T_{max} 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 pharmacokinetic 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 C_{max}, AUC and T_{max} 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 C_{max} for ARTHROTEC® 75 was significantly lower than that for diclofenac alone. Misoprostol acid C_{max} 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 C_{max} for either components."

**APPEARS THIS WAY
ON ORIGINAL**

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 bioequivalence 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 C_{max} 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.
<u>Diclofenac/Placebo</u>	AUC(0-∞)	103.3%	(96.5%, 110.5%)
<u>Voltaren (U.S.)</u>	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.

**APPEARS THIS WAY
ON ORIGINAL**

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 (C_{max}), time to C_{max} (t_{max}), and area under the curve from time 0 to infinity [$AUC(0-\infty)$] were determined for each treatment. The PK parameters $AUC(0-\infty)$ and C_{max} 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 vs. Searle Searle-? vs. Geigy U.S.; Searle vs. Geigy U.S.

Overall, assay method and quality control data are acceptable.

Results: The firm provided the following:

<u>Treatment (N=24)</u>	<u>C_{max}</u> (ng/ml)	<u>t_{max}</u> (hr)	<u>AUC(0-∞)</u> (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 C_{max} and t_{max} 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 C_{max} and t_{max} data for subject #16.

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

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

**APPEARS THIS WAY
ON ORIGINAL**

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 (C_{max}), time to C_{max} (t_{max}), and area under the curve (AUC) for diclofenac and misoprostol acid were determined for each treatment. AUC and C_{max} 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.