CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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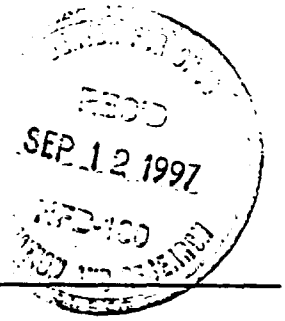
CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-607 Submission Date:August 7th 1997
Arthrotec™ Tablets
Diclofenac sodium/Misoprostol
50mg/200mcg and 75 mg/200 mcg
G.D.Searle
Skokie, IL 60077



Reviewer: Lydia C. Kaus, Ph.D.
Type of Submission: Additional studies in support of original NDA

SYNOPSIS:
The sponsors have completed two pharmacokinetic bioequivalence studies in response to the 3/26/97 letter sent to the sponsors from HFD-180. Specifically the following was stated in the letter:

"The diclofenac in the Arthrotec formulations is not the same as the approved diclofenac, Voltaren. To establish the efficacy of the diclofenac in the Arthrotec formulations proposed for marketing, adequate well-controlled clinical studies providing substantial evidence of safety and efficacy or data that demonstrate bioequivalence to Voltaren must be provided.

.....

While evidence from both Cytotec and Arthrotec studies are cited to support efficacy, bioequivalence of the Arthrotec formulation "to be marketed" to marketed Cytotec must be demonstrated to qualify the Cytotec studies in support of the Arthrotec NDA."

RECOMMENDATION:
Since Cytotec and Voltaren are not necessarily given together because of different frequency of dosing (see the current labeling for the individual drugs), comparisons were made for Arthrotec™50 and Arthrotec™75 to Voltaren and Cytotec when given alone.

1. 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 given alone. 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 or Cytotec.

2. Arthrotec™50 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 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 or Cytotec.

The Medical Reviewer should judge these results in the context of the impact on the efficacy and safety of Arthrotec. Please note that no concentration-response relationship for either diclofenac or misoprostol has been submitted to the Agency, therefore any differences in misoprostol or diclofenac plasma levels have to be judged empirically. Lack of bioequivalence or acceptance of

different bioequivalence criteria could be considered, if satisfactory clinically equivalent effects have been shown with formulations that are different in their rate and extent of absorption.

3. The sponsors request for the following dissolution method for misoprostol is acceptable:

/S/ 9/12/97

APPEARS THIS WAY
ON ORIGINAL

Lydia C. Kaus, M.S., Ph.D.
Team Leader, Gastrointestinal and Coagulation Drug Products, Division of Pharmaceutical Evaluation II.

FT initialed by /S/ 9/12/97
Mei-Ling Chen, Ph.D.
Director, DPEII

cc:NDA 20-607, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

APPEARS THIS WAY
ON ORIGINAL

Protocol NN2-97-02-359

Title: Clinical study for an open-label, randomized, five period crossover study to compare the bioequivalence of Arthrotec 75 to marketed Voltaren™ and Cytotec™ tablets in healthy adult subjects under fasting conditions.

OBJECTIVE

1. To assess the bioequivalence of Arthrotec™ 75 BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately
2. To assess the bioequivalence of Arthrotec™ 75 BID relative to coadministration of Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID
3. To assess the bioequivalence of coadministered Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately.

METHODS:

Study Design:

This was an open-label, four treatment, five period crossover study in healthy adult volunteers. Fifty-six 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	Treatment Days 29-32
1	14	A	D	B	C	A
2	14	B	A	C	D	B
3	14	C	B	D	A	C
4	14	D	C	A	B	D

A = Arthrotec 75 BID
B = Voltaren 75 mg BID **Reference arm for diclofenac**
C = Cytotec 200 mcg BID **Reference arm for misoprostol**
D = Voltaren 75 mg BID + Cytotec 200 mcg BID coadministration

Subjects:
Fifty-six 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, 25 and 32. Subjects fasted for at least 2 hours prior to and 2 hours after the doses on days 1-3, 8-10, 15-17, 22-24, and 29-32. Because of protocol deviations concerning processing of the misoprostol acid plasma samples, pharmacokinetic analyses were exlcuded from data collected during the first period. After the evening dose on Days 3, 10, 17, 24 and 31, subjects remained in an upright posture for at least two hours after dosing. 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:

- enteric-coated core of diclofenac sodium 75 mg with an containing misoprostol 200 mcg

- enteric-coated tablets containing diclofenac sodium 75 mg (Voltaren manufactured by Geigy Pharmaceuticals for distribution in the US).

- tablets containing misoprostol 200 mcg (Cytotec, manufactured by Searle for distribution in the US).

Pharmacokinetic Analysis:
Tmax, tlag, Cmax, Cmin, AUCo-lqc and AUCo-inf, AUCo-12hr(diclofenac) and AUCo-inf, AUC0-4hr(misoprostol) were reported.

Diclofenac:

Misoprostol acid:

APPEARS THIS WAY
ON ORIGINAL

RESULTS from 8/22/97 communication:

Statistical Analysis of diclofenac pharmacokinetic data Study 359:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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
AUClast (ng.hr/mL)	1901.29 (27)	2278.88 (30)	0.83	0.77,0.89	Fail
Cmax (ng/mL)	1582.90 (38)	2166.5 (36)	0.71	0.63,0.80	Fail
Athrotec (test) vs. Voltaren (reference) given with Cytotec					
AUC0-12 (ng.hr/mL)	2181.44 (34)	2326.71 (31)	0.90	0.84,0.97	Pass
AUClast (ng.hr/mL)	1901.29 (27)	2139.43 (35)	0.90	0.84,0.97	Pass
Cmax (ng/mL)	1582.90 (38)	2122.92 (40)	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
AUClast (ng.hr/mL)	2139.43 (35)	2278.88 (30)	0.92	0.86,0.99	Pass
Cmax (ng/mL)	2122.92 (40)	2166.5 (36)	0.94	0.83,1.06	Fail

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
MISOPROSTOL ACID COMPONENT Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUClast (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
Cmax (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUClast (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	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))	1.09	1.02,1.18	Pass
AUClast (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
Cmax (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC0-4 denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC_{0-12} for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC_{0-12} represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUCinf is less reliable where the data points on the terminal phase of the curve are not well represented.

RESULTS from 9/10/97 communication:

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
MISOPROSTOL ACID COMPONENT Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUClast (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
Cmax (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUClast (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	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))	1.09	1.02,1.18	Pass
AUClast (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
Cmax (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC0-4 denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC_{0-12} for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC_{0-12} represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUCinf is less reliable where the data points on the terminal phase of the curve are not well represented.

RESULTS from 9/10/97 communication:

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol

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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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:

- 11 mm combination tablets containing an aqueous enteric-coated core of diclofenac sodium 50 mg with an outer mantle 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:
Tmax, tlag, Cmax, Cmin, AUCo-lqc and AUCo-inf, AUCo-12hr(diclofenac) andAUC0-inf and AUC0-4hr(misoprostol) were reported.

Analytical Methods:

RESULTS

Statistical Analysis of diclofenac pharmacokinetic data, Study 360:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
DICLOFENAC COMPONENT Arthrotec (test) vs. Voltaren alone (reference)					
AUC0-12 (ng.hr/mL)	1175.85(29)	1324.64(32)	0.89	0.81,0.98	Pass
AUClast (ng.hr/mL)	1149.95 (29)	1290.70 (33)	0.90	0.81,0.99	Pass
Cmax (ng/mL)	950.98 (45)	1294.2 (46)	0.72	0.61,0.84	Fail
Athrotec (test) vs. Voltaren (reference) given with Cytotec					
AUC0-12 (ng.hr/mL)	1175.85(29)	1181.02(35)	1.04	0.94,1.14	Pass
AUClast (ng.hr/mL)	1901.29 (27)	1144.40 (36)	1.05	0.95,1.16	Pass
Cmax (ng/mL)	1582.90 (38)	1190.39 (50)	0.84	0.72,0.98	Fail
Voltaren (test) given with Cytotec vs. Voltaren alone (reference)					
AUC0-12 (ng.hr/mL)	1181.02(35)	1324.64(32)	0.86	0.78,0.95	Fail
AUClast (ng.hr/mL)	1290.70 (33)	1290.70 (33)	0.86	0.78,0.94	Fail
Cmax (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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
MISOPROSTOL ACID COMPONENT Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	400.88(28)	451.61(30)	0.89	0.84,0.95	Pass
AUClast (pg.hr/mL)	367.89 (32)	419.75 (34)	0.88	0.83,0.95	Pass
Cmax (pg/mL)	607.61 (35)	714.83 (34)	0.84	0.78,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	400.88(28)	419.38(30)	0.96	0.91,1.02	Pass
AUClast (pg.hr/mL)	367.89 (32)	391.01 (31)	0.94	0.87,1.00	Pass
Cmax (pg/mL)	607.61 (35)	631.64 (36)	0.96	0.89,1.03	Pass
Voltaren given with Cytotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	419.38(30)	451.61(30)	0.93	0.87,0.99	Pass
AUClast (pg.hr/mL)	391.01 (31)	419.75 (34)	0.95	0.88,1.01	Pass
Cmax (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 Cmax 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:

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	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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	0.6327536	0.80016	0.0706409	51	93

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		(difference)		
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	0.0715534	51	93

Study 359 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 rati	Interval		(difference)		
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	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
AUC4	6.122448	6.01605	-0.1064	-0.17197	-0.04083	455.9794	409.9561	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	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
AUC4	6.028676	6.01605	-0.01263	-0.07861	0.053363	415.1649	409.9561	0.987454	0.9243966	1.05481	0.0397309	51	96
AUCL	5.965989	5.961415	-0.00457	-0.07583	0.06668	389.9384	388.1592	0.995437	0.9269768	1.06895	0.042901	51	96
CMAX	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		(difference)		
AUC4	6.028676	6.122448	0.093772	0.027783	0.15976	415.1649	415.1649	1.098309	1.0281731	1.17323	0.0397309	51	96
AUCL	6.073294	5.965989	-0.10731	-0.17856	-0.03605	434.1083	389.9384	0.898251	0.836475	0.96459	0.042901	51	96
CMAX	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	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
AUC12	7.14592	7.031967	-0.11395	-0.2091	-0.0188	1268.918	1132.256	0.8923	0.8113135	0.98137	0.0572155	47	85
AUCL	7.117644	7.009005	-0.10864	-0.20661	-0.01066	1233.541	1106.553	0.897054	0.8133331	0.98939	0.0589158	47	85
CMAX	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	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
AUC12	6.99547	7.031967	0.036497	-0.05952	0.132513	1091.676	1132.256	1.037172	0.9422181	1.14169	0.0577373	47	85
AUCL	6.962336	7.009005	0.046669	-0.0522	0.145539	1056.098	1106.553	1.047776	0.9491392	1.15666	0.0594531	47	85
CMAX	6.936692	6.762873	-0.17382	-0.32853	-0.0191	1029.359	865.1245	0.84045	0.7199779	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 rati	Interval		(difference)		
AUC12	7.14592	6.99547	-0.15045	-0.24563	-0.05527	1268.918	1091.676	0.860321	0.7822114	0.94623	0.0572347	47	85
AUCL	7.117644	6.962336	-0.15531	-0.25332	-0.0573	1233.541	1056.098	0.856151	0.7762219	0.94431	0.0589355	47	85
CMAX	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 rati	Interval		(difference)		
AUC4	6.061401	5.949839	-0.11156	-0.16957	-0.05355	428.9759	383.6915	0.894436	0.8440281	0.94785	0.0348906	47	87
AUCL	5.974725	5.852956	-0.12177	-0.19081	-0.05273	393.3598	348.2623	0.885353	0.8262891	0.94864	0.0415275	47	87
CMAX	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 rati	Interval		(difference)		
AUC4	5.989754	5.949839	-0.03991	-0.09743	0.017596	399.3162	383.6915	0.960871	0.9071699	1.01775	0.0345918	47	87
AUCL	5.918932	5.852956	-0.06598	-0.13443	0.002474	372.0142	348.2623	0.936153	0.874217	1.00248	0.0411719	47	87
CMAX	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 rati	Interval		(difference)		
AUC4	6.061401	5.989754	-0.07165	-0.12919	-0.0141	428.9759	428.9759	0.930859	0.8788066	0.986	0.0346114	47	87
AUCL	5.974725	5.918932	-0.05579	-0.12428	0.012697	393.3598	372.0142	0.945735	0.8831308	1.01278	0.0411952	47	87
CMAX	6.519337	6.387441	-0.1319	-0.20666	-0.05714	678.1289	594.3334	0.876431	0.8132992	0.94446	0.0449665	47	87

9/11 7

Study 359 - Arthrotec 75 mg

DICLOFENAC

Study 359 Arthrotec vs. Voltaren

	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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

	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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

	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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

	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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		(difference)		
AUC4	6.028685	6.016611	-0.01207	-0.07814	0.053994	415.1689	410.1861	0.987998	0.9248327	1.05548	0.0397789	51	96
AUCinf	6.08179	6.077802	-0.00399	-0.08618	0.078208	437.8122	436.0696	0.99602	0.917425	1.08135	0.0494575	51	90
CMAX	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		(difference)		
AUC4	6.122424	6.028685	-0.09374	-0.15981	-0.02767	455.9687	455.9687	0.910521	0.8523083	0.97271	0.0397789	51	96
AUCinf	6.185707	6.08179	-0.10392	-0.18708	-0.02076	485.7562	437.8122	0.9013	0.8293788	0.97946	0.0500382	51	90
CMAX	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

SEP 12 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-607 Submission Date:August 7th 1997
Arthrotec™ Tablets
Diclofenac sodium/Misoprostol
50mg/200mcg and 75 mg/200 mcg
G.D.Searle
Skokie, IL 60077

Reviewer: Lydia C. Kaus, Ph.D.
Type of Submission: Additional studies in support of original NDA

SYNOPSIS:

The sponsors have completed two pharmacokinetic bioequivalence studies in response to the 3/26/97 letter sent to the sponsors from HFD-180. Specifically the following was stated in the letter:

"The diclofenac in the Arthrotec formulations is not the same as the approved diclofenac, Voltaren. To establish the efficacy of the diclofenac in the Arthrotec formulations proposed for marketing, adequate well-controlled clinical studies providing substantial evidence of safety and efficacy or data that demonstrate bioequivalence to Voltaren must be provided.

.....

While evidence from both Cytotec and Arthrotec studies are cited to support efficacy, bioequivalence of the Arthrotec formulation "to be marketed" to marketed Cytotec must be demonstrated to qualify the Cytotec studies in support of the Arthrotec NDA."

RECOMMENDATION:

Since Cytotec and Voltaren are not necessarily given together because of different frequency of dosing (see the current labeling for the individual drugs), comparisons were made for Arthrotec™50 and Arthrotec™75 to Voltaren and Cytotec when given alone.

1. 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 given alone. 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 or Cytotec.

2. Arthrotec™50 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 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 or Cytotec.

The Medical Reviewer should judge these results in the context of the impact on the efficacy and safety of Arthrotec. Please note that no concentration-response relationship for either diclofenac or misoprostol has been submitted to the Agency, therefore any differences in misoprostol or diclofenac plasma levels have to be judged empirically. Lack of bioequivalence or acceptance of

different bioequivalence criteria could be considered, if satisfactory clinically equivalent effects have been shown with formulations that are different in their rate and extent of absorption.

3. The sponsors request for the following dissolution method for misoprostol is acceptable:

/S/ 11/24/97

- APPEARS THIS WAY
ON ORIGINAL

Lydia C. Kaus, M.S., Ph.D.
Team Leader, Gastrointestinal and Coagulation Drug Products, Division of Pharmaceutical Evaluation II.

FT initialed by /S/ 9/2/97
Mei-Ling Chen, Ph.D.
Director, DPEII

cc:NDA 20-607, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

APPEARS THIS WAY
ON ORIGINAL

Protocol NN2-97-02-359

Title: Clinical study for an open-label, randomized, five period crossover study to compare the bioequivalence of Arthrotec 75 to marketed Voltaren™ and Cytotec™ tablets in healthy adult subjects under fasting conditions.

OBJECTIVE

1. To assess the bioequivalence of Arthrotec™ 75 BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately
2. To assess the bioequivalence of Arthrotec™ 75 BID relative to coadministration of Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID
3. To assess the bioequivalence of coadministered Voltaren™ 75 mg BID and Cytotec™ 200 mcg BID relative to Voltaren™ 75 mg BID or Cytotec™ 200 mcg BID given separately.

METHODS:

Study Design:

This was an open-label, four treatment, five period crossover study in healthy adult volunteers. Fifty-six 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	Treatment Days 29-32
1	14	A	D	B	C	A
2	14	B	A	C	D	B
3	14	C	B	D	A	C
4	14	D	C	A	B	D

A = Arthrotec 75 BID
B = Voltaren 75 mg BID **Reference arm for diclofenac**
C = Cytotec 200 mcg BID **Reference arm for misoprostol**
D = Voltaren 75 mg BID + Cytotec 200 mcg BID coadministration

Subjects:
Fifty-six 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, 25 and 32. Subjects fasted for at least 2 hours prior to and 2 hours after the doses on days 1-3, 8-10, 15-17, 22-24, and 29-32. Because of protocol deviations concerning processing of the misoprostol acid plasma samples, pharmacokinetic analyses were exlcuded from data collected during the first period. After the evening dose on Days 3, 10, 17, 24 and 31, subjects remained in an upright posture for at least two hours after dosing. 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 75 mg with an containing misoprostol 200 mcg

- enteric-coated tablets containing diclofenac sodium 75 mg (Voltaren manufactured by Geigy Pharmaceuticals for distribution in the US).

- tablets containing misoprostol 200 mcg (Cytotec, manufactured by Searle for distribution in the US).

Pharmacokinetic Analysis:
Tmax, tlag, Cmax, Cmin, AUCo-lqc and AUCo-inf, AUCo-12hr(diclofenac) and AUCo-inf, AUC0-4hr(misoprostol) were reported.

Analytical Method:

RESULTS from 8/22/97 communication:

Statistical Analysis of diclofenac pharmacokinetic data Study 359:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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
AUClast (ng.hr/mL)	1901.29 (27)	2278.88 (30)	0.83	0.77,0.89	Fail
Cmax (ng/mL)	1582.90 (38)	2166.5 (36)	0.71	0.63,0.80	Fail
Athrotec (test) vs. Voltaren (reference) given with Cytotec					
AUC0-12 (ng.hr/mL)	2181.44 (34)	2326.71 (31)	0.90	0.84,0.97	Pass
AUClast (ng.hr/mL)	1901.29 (27)	2139.43 (35)	0.90	0.84,0.97	Pass
Cmax (ng/mL)	1582.90 (38)	2122.92 (40)	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
AUClast (ng.hr/mL)	2139.43 (35)	2278.88 (30)	0.92	0.86,0.99	Pass
Cmax (ng/mL)	2122.92 (40)	2166.5 (36)	0.94	0.83,1.06	Fail

Statistical Analysis of misoprostol acid pharmacokinetic data:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
MISOPROSTOL ACID COMPONENT Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	492.70(44)	0.90	0.84,0.97	Pass
AUClast (pg.hr/mL)	419.18 (37)	473.28 (46)	0.89	0.83,0.96	Pass
Cmax (pg/mL)	677.31 (62)	823.96 (60)	0.81	0.71,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	438.23(34)	442.29(37)	0.99	0.92,1.06	Pass
AUClast (pg.hr/mL)	419.18 (37)	459.18 (37)	1.00	0.93,1.07	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))	1.09	1.02,1.18	Pass
AUClast (pg.hr/mL)	459.18 (37)	473.28 (46)	0.90	0.84,0.96	Pass
Cmax (pg/mL)	725.92 (58)	823.96 (60)	0.90	0.80,1.02	Pass

Note that AUC0-4 denotes the area-under-the curve measured from 0 to 4 hours and AUCL denotes the area-under-the curve measured up to the last sampling time point

AUC_{0-12} for the diclofenac measurements is a better representation of the data as far as bioequivalence testing is concerned. AUC_{0-12} represents the dosing interval under multiple dosing and is the accepted parameter to test in bioequivalence testing. AUCinf is less reliable where the data points on the terminal phase of the curve are not well represented.

RESULTS from 9/10/97 communication:

The sponsors sent a letter dated 9/10/97 explaining that certain changes were made to the database. Specifically, changes were made to data from subject 18 (diclofenac, day 18, Arthrotec arm), subject 26 (misoprostol, Day 25, Arthrotec arm) and subject 30 (misoprostol

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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
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:
Tmax, tlag, Cmax, Cmin, AUCo-lqc and AUCo-inf, AUCo-12hr(diclofenac) andAUC0-inf and AUC0-4hr(misoprostol) were reported.

Analytical Methods:

RESULTS

Statistical Analysis of diclofenac pharmacokinetic data, Study 360:

Pharmacokinetic parameter	MEAN (%CV) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
DICLOFENAC COMPONENT Arthrotec (test) vs. Voltaren alone (reference)					
AUC0-12 (ng.hr/mL)	1175.85(29)	1324.64(32)	0.89	0.81,0.98	Pass
AUClast (ng.hr/mL)	1149.95 (29)	1290.70 (33)	0.90	0.81,0.99	Pass
Cmax (ng/mL)	950.98 (45)	1294.2 (46)	0.72	0.61,0.84	Fail
Athrotec (test) vs. Voltaren (reference) given with Cytotec					
AUC0-12 (ng.hr/mL)	1175.85(29)	1181.02(35)	1.04	0.94,1.14	Pass
AUClast (ng.hr/mL)	1901.29 (27)	1144.40 (36)	1.05	0.95,1.16	Pass
Cmax (ng/mL)	1582.90 (38)	1190.39 (50)	0.84	0.72,0.98	Fail
Voltaren (test) given with Cytotec vs. Voltaren alone (reference)					
AUC0-12 (ng.hr/mL)	1181.02(35)	1324.64(32)	0.86	0.78,0.95	Fail
AUClast (ng.hr/mL)	1290.70 (33)	1290.70 (33)	0.86	0.78,0.94	Fail
Cmax (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) Test	Reference	Geometric mean Ratio (Test/Reference)	90% Confidence interval	Pass/Fail
MISOPROSTOL ACID COMPONENT Arthrotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	400.88(28)	451.61(30)	0.89	0.84,0.95	Pass
AUClast (pg.hr/mL)	367.89 (32)	419.75 (34)	0.88	0.83,0.95	Pass
Cmax (pg/mL)	607.61 (35)	714.83 (34)	0.84	0.78,0.91	Fail
Athrotec (test) vs. Voltaren given with Cytotec (reference)					
AUC0-4 (pg.hr/mL)	400.88(28)	419.38(30)	0.96	0.91,1.02	Pass
AUClast (pg.hr/mL)	367.89 (32)	391.01 (31)	0.94	0.87,1.00	Pass
Cmax (pg/mL)	607.61 (35)	631.64 (36)	0.96	0.89,1.03	Pass
Voltaren given with Cytotec (test) vs. Cytotec alone (reference)					
AUC0-4 (pg.hr/mL)	419.38(30)	451.61(30)	0.93	0.87,0.99	Pass
AUClast (pg.hr/mL)	391.01 (31)	419.75 (34)	0.95	0.88,1.01	Pass
Cmax (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 Cmax 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	90% Confidence		std error	n	df (MSE)
	reference	test		interval		reference	test	mean rati	interval		(difference)		
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	0.6327536	0.80016	0.0706409	51	93

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		(difference)		
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	0.6718736	0.85221	0.0716534	51	93

Study 359 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 rati	interval		(difference)		
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	90% Confidence		std error	n	df (MSE)
	reference	test		interval		reference	test	mean rati	interval		(difference)		
AUC4	6.122448	6.01605	-0.1064	-0.17197	-0.04083	455.9794	409.9561	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

udy 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		(difference)		
JC4	6.028676	6.01605	-0.01263	-0.07861	0.053363	415.1649	409.9561	0.987454	0.9243966	1.05481	0.0397309	51	96
JCL	5.965989	5.961415	-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

udy 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		(difference)		
JC4	6.028676	6.122448	0.093772	0.027783	0.15976	415.1649	415.1649	1.098309	1.0281731	1.17323	0.0397309	51	96
JCL	6.073294	5.965989	-0.10731	-0.17856	-0.03605	434.1083	389.9384	0.898251	0.836475	0.96459	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

udy 360 Arthrotec vs. Voltaren

	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
JC12	7.14592	7.031967	-0.11395	-0.2091	-0.0188	1268.918	1132.256	0.8923	0.8113135	0.98137	0.0572155	47	85
JCL	7.117644	7.009005	-0.10864	-0.20681	-0.01066	1233.541	1106.553	0.897054	0.8133331	0.98939	0.0589168	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

udy 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 rati	Interval		(difference)		
JC12	6.99547	7.031967	0.036497	-0.05952	0.132513	1091.676	1132.256	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	1.047776	0.9491392	1.15666	0.0594531	47	85
MAX	6.936692	6.762873	-0.17382	-0.32853	-0.0191	1029.359	865.1245	0.84045	0.7199779	0.98108	0.0930359	47	85

udy 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 rati	Interval		(difference)		
IC12	7.14592	6.99547	-0.15045	-0.24563	-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
AX	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

udy 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 rati	Interval		(difference)		
IC4	6.061401	5.949839	-0.11158	-0.16957	-0.05355	428.9759	383.6915	0.894436	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	0.0415276	47	87
AX	6.519337	6.346648	-0.17269	-0.24805	-0.09733	678.1289	570.5768	0.841399	0.7803194	0.90726	0.0453292	47	87

udy 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 rati	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
AX	6.387441	6.346648	-0.04079	-0.11551	0.033924	594.3334	570.5768	0.960028	0.890912	1.03451	0.044941	47	87

udy 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 rati	Interval		(difference)		
IC4	6.061401	5.989754	-0.07165	-0.12919	-0.0141	428.9759	428.9759	0.930859	0.8788066	0.986	0.0346114	47	87
ICL	5.974725	5.918932	-0.05579	-0.12428	0.012697	393.3598	372.0142	0.945735	0.8831308	1.01278	0.0411952	47	87
AX	6.519337	6.387441	-0.1319	-0.20666	-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	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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	ls mean (log)		difference	90% Confidence		geometric mean		geometric	90% Confidence		std error	n	df (MSE)
	reference	test		Interval		reference	test	mean rati	Interval		(difference)		
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

tudy 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 ratl	Interval		(difference)		
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	436.0696	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

tudy 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 ratl	Interval		(difference)		
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

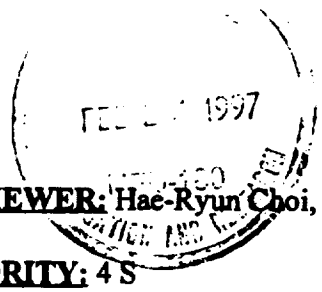
FEB 2 4 1997

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 $AUC_{(0-lqc)}$ 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 Cmax (Cmax 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 Cmax (Cmax 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 Cmax (Cmax 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 Cmax.

Misoprostol Component: Bioequivalency has been demonstrated between misoprostol in Arthrotec and marketed Cytotec for misoprostol acid AUC, but not for misoprostol acid Cmax (Cmax 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 Cmax.

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(lqc) 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 Cmax and (89.6%, 107.8%) for AUC(0-lqc). 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-lqc) and Cmax 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 Cmax.

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:

<u>Diclofenac</u>

<u>Misoprostol</u>

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 Cmax. 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 Cmax 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 Cmax.

/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 LCK 11/8/96
Division of Pharmaceutical Evaluation II, HFD-870

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

APPEARS THIS WAY
ON ORIGINAL

B. 75 mg Strength

Combo Diclofenac (To be marketed)	vs.	Combo Diclofenac	vs.	Ciba-Geigy Diclofenac
AUC	=	AUC	=	AUC
Cmax	=	Cmax	<<	Cmax
		[ratio 'Ciba) = 73.4%, 90% C.I. = 58.5%, 92.1%]		

APPEARS THIS WAY 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 Diclofenac/placebo	vs.	Ciba-Geigy Diclofenac
AUC	=	AUC
Cmax [Ratio (Searle/Ciba) = 89.4%, 90% C.I. = 66.2%, 120.5%]	<	Cmax

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY 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 [Ratio =87.8%, 90% C.I. = 75.2%, 102.6%]	>	Cmax

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 [Ratio 'Cytotec) =106.8%, 90% C.I. = 90.0%, 126.8%]	>	Cmax

Conclusion:

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

/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

APPEARS THIS WAY
ON ORIGINAL

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 Cmax; Arthrotec 50 and Cytotec alone were also bioequivalent with respect to misoprostol acid AUC and Cmax. Arthrotec 50 was shown to be bioequivalent to Voltaren + Cytotec coadministration with respect to diclofenac AUC, misoprostol acid AUC and Cmax. However, bioequivalency of the two treatments could not be demonstrated for diclofenac Cmax (Cmax 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 Cmax 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 Cmax (Cmax ratio = 73.4%, 90% C.I. = 58.5%, 92.1%). Mean misoprostol acid Cmax 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 Cmax (Cmax 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 Cmax; diclofenac AUC ratio = 108.6%, 90% C.I. = 93.6 - 125.9%, diclofenac Cmax 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 Cmax ratio = 113.4%, 90% C.I. = 95.5 - 134.6%, .espectively.

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 while for With the Arthrotec 50 tablets, there is no direct link between the proposed and the Instead, the proposed were indirectly linked to the via the Arthrotec tablets, which were nearly identical in formulation to The differences being in the misoprostol and site(s) of manufacture was the original formulation used in early clinical efficacy/safety trials. 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 were bioequivalent to the reference organic diclofenac 50 mg/duplex misoprostol 200 mcg combination tablets with respect to both diclofenac and misoprostol acid AUC and Cmax.

In comparison of 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 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 proposed product 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 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 chemical supplied The proposed and contains diclofenac chemical supplied by It was shown that the tablets manufactured at were bioequivalent to the tablets manufactured at 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 Cmax (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 Cmax (90% C.I.= 41.6%, 59.9%), respectively; time to peak concentration (tmax) 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 treatments 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 Cmax (Cmax ratio = 86.5%, 90% C.I. = 71.9%, 103.9%). Under fed conditions, mean diclofenac AUC and Cmax 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%, Cmax 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 Cmax (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 Cmax (90% C.I.= 34.9%, 48.6%), respectively, as compared to fasted conditions. Tmax 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 Cmax 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 [Cmax(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 Cmax under fasted conditions.

The diclofenac chemical in diclofenac/placebo tablets supplied by and the diclofenac chemical in diclofenac/placebo tablets used in previous clinical trials 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 Instead, the proposed were indirectly compared to the marketed Arthrotec tablets which were nearly identical in formulation to were shown to be bioequivalent. However, the proposed was not bioequivalent to the formulation in terms of diclofenac Cmax. The proposed was not bioequivalent to the formulation in terms of misoprostol acid Cmax. Furthermore, the proposed 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 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 in consultation with the Medical Division.

2. Bioequivalence study with following three arms: to be marketed (formulation and manufacturing) with full new in date production lot, and marketed Cytotec.

With the Arthrotec 75 tablets, the proposed was shown to be bioequivalent to the 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.

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APPENDIX:

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 E_1 (PGE_1) 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 t1/2 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 t1/2, Cmax 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 in increased without substantial changes in misoprostol elimination t1/2.

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 Cmax. However, the three subject who had the lowest anti-pyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and Cmax 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	Dico/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	Jun 1992	F9101/034	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	F9308/078	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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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

Clinical studies have also been conducted with both the proposed enteric coating and the enteric coating.

The enteric coating formulation was used in these clinical studies:

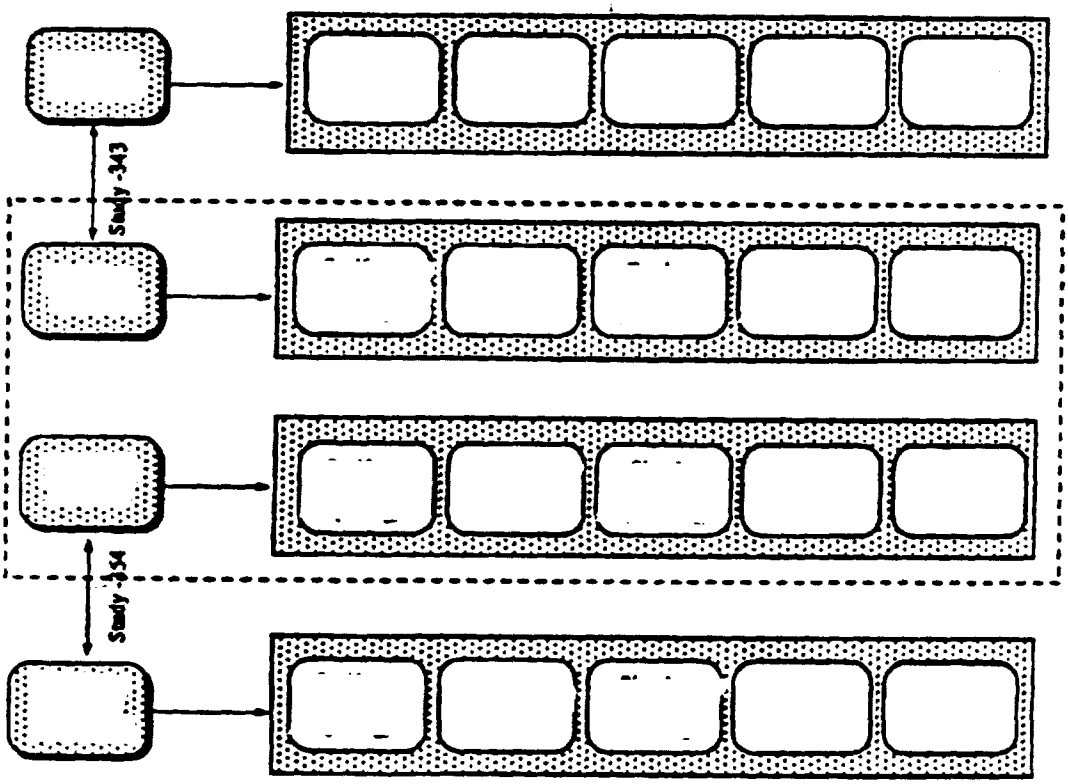
IN2-89-02-289	IN2-89-02-292	EN2-88-02-293
IN2-89-02-296	IN2-89-02-297	IN2-89-02-298
EN2-89-02-302	NN2-89-02-303	EN2-90-02-304
IN2-90-02-305	EN2-91-02-306	IN2-89-01-310
NN2-89-02-316	IN2-90-02-321	NN2-90-02-329
NN2-91-02-332	NN2-91-02-338	NN2-91-02-342
NN2-91-02-343	NN2-93-02-345	NN2-95-02-354

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

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).

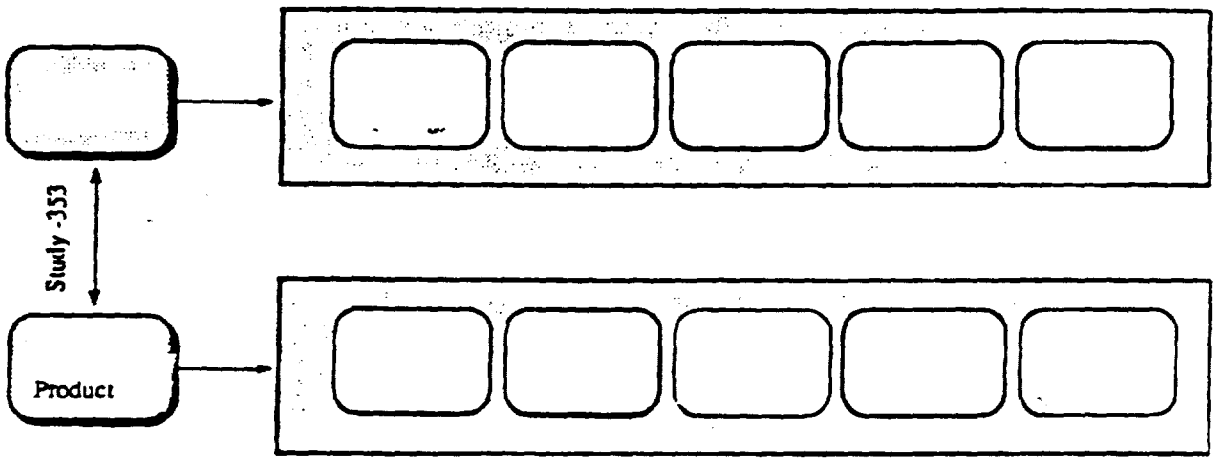
The following figure shows the bioequivalency link between and the proposed marketed



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