Table 5. Comparison of Most Commonly Report Adverse Events from Phase I and Dental Pain Studies from Arthrotec® NDA*, Study 359 and Study 360

event	Arthrotec® ISS** (%)	Study 359 (%)	Study 360 (%)
headache	10.9	8	6
abdominal pain	7.7	12	16
menstrual disorder	6.7	0	2
nausea	6.0	10	10
uterine cramping	5.3	0	2
diarrhea	5.2	6	6
dizziness	4.7	8	6
rhinitis	4.5	6	4
coughing	1.5	4	0
dyspepsia	3.0	2	6
vomiting	1.2	2	6
pain	1.0	0	6

* Arthrotec® NDA, ISS Table 8A, Pages 103-109 of 420
** Phase I and Dental Pain Studies

APPEARS THIS WAY
ON ORIGINAL

APPENDIX C

Table 9. Frequency of Serious Adverse Events in Patients Who Received Arthrotec® Reported by Body System; Ex-U.S. Phase IV Clinical Trials and Post-Marketing Experience

Gastrointestinal System Disorders	ISS*	Safety Update
Abdominal pain	0	2
Diarrhea	1	4
Nausea	2	3
Flatulence	0	1
Dyspepsia	0	1
Vomiting	0	4
GI hemorrhage	7	21
Hemorrhage rectum	1	4
Melena	0	3
Gastritis	0	2
Gastric ulcer	1	5
Hematemesis	1	2
Duodenal ulcer perforated	6	7 /
Duodenal ulcer	1	5
Gastric ulcer hemorrhagic	1	3
Duodenal ulcer hemorrhagic	1	1
Colitis	0	1
Gastric ulcer perforated	1	1
Intestinal ulceration perforated	0	1
Esophageal ulceration	1	1
Pancreatitis	0	1
Peptic ulcer	0	1
Peptic ulcer hemorrhagic	0	1
Peptic ulcer perforated	1	1
GI neoplasm benign	0	1
Body System Total	25	77

*Arthrotec® NDA, ISS, Table 36, Page 420 of 420 (1)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

DEC - 2 1997

NDA 20-607 CHEM.REVIEW: #5 REVIEW DATE: October 27, 1997

SUBMISSION TYPE

	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM LET ST
ORIG.	22Dec95	26Dec95	16Jan96		1
AMENDMENTS					
BC(Secifarma)	27Jun96	02Jul96	10Jul96		1
BZ(Stability)	23Feb96	26Feb96	05Mar96		1
ORIG.(EA)	22Dec95	26Dec95	16Jan96		2
BC (EA)	22Jan97	24Jan97	08Feb97		3
BC	03Feb97	04Feb97	19Feb97		4
BC	14Oct97	15Oct97	24Oct97		5

NAME & ADDRESS OF APPLICANT:
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

DRUG PRODUCT NAME
Proprietary: Arthrotec™
Nonproprietary/USAN: diclofenac sodium/misoprostol
Code Name/#:
Chem.Type/Ther.Class: 4S

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:
diclofenac sodium: nonsteroidal anti-inflamatory (NSAID)
misoprostol: antisecrretory/mucoprotectant prostaglandin E_1

treatment of the signs and symptoms of osteoartheritis and rheumatoid artheritis.

DOSAGE FORM: tablet
STRENGTHS: 50 mg diclofenac sodium/200 µg misoprostol
75 mg diclofenac sodium/200 µg misoprostol

ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1

SUPPORTING DOCUMENTS:
See Chemistry Review #1.

RELATED DOCUMENTS (if applicable):
See Chemistry Review #1.

APPEARS THIS WAY
ON ORIGINAL

CONSULTS:
All consults have been completed and are acceptable.

Division	Consult Date	Status	Comments
1. Division of Manufacturing and Product Quality HFD-324	02Feb96 14Jun96 (Compl)	**Acceptable**	has withdrawn as manufacturer of the drug substance diclofenac sodium (see BC Amendment 27Jun96)
2. Division of Biometrics II HFD-720 (Dr. Milton Fan)	14Mar96 23Oct96 (Compl)	**Completed**	Expiration dating two dosage strengths, 50/200 and 75/200, and six container-closures
3. Division of Pharmaceutical Evaluation II, HFD-870 (Dr. Lydia Kauss)	15Feb96 02Sep96 (See CR#4)	**Completed**	Dissolution Spec proposal to perform dissolution on enteric coated
4. Labeling and Nomenclature Committee, HFD-530	02Feb96 06May96 (Let)	**Acceptable**	ARTHROTEC was originally considered unacceptable dur to similarity with AMPOTEC.

(Dr. Dan Boring)

REMARKS/COMMENTS:
Searle is responding to the "approvable" action letter of 17Sep97.

CONCLUSIONS & RECOMMENDATIONS:
This NDA may be approved (AP).

/S/ 1/24/97

George T. Chen, Ph.D.
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 12/2/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-607
HFD-180/Division File
HFD-180/BStrongin
HFD-180/GChen
R/D Init by: Eduffy/11-15-97
GC/dob **F/T 11-20-97**/WP: c:\wpfiles\chem\N\20607710.5GC

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA : 20-607 **CHEM.REVIEW #:** 4 **REVIEW DATE:** September 2, 1997

SUBMISSION TYPE

	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LET	ST
ORIGINAL	22Dec95	26Dec95	16Jan96		1		
AMENDMENT							
BC(Secifarma)	27Jun96	02Jul96	10Jul96		1		
BZ(Stability)	23Feb96	26Feb96	05Mar96		1		
ORIGINAL[EA]	22Dec95	26Dec95	16Jan96		2		
BC (EA)	22Jan97	24Jan97	08Feb97	13Feb97	3		
BC	03Feb97	04Feb97	19Feb97		4		

NAME & ADDRESS OF APPLICANT:
G.D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

DRUG PRODUCT NAME
Proprietary: Arthrotec ™
Nonproprietary/USAN: diclofenac sodium/misoprostol
Code Name/#:
Chem.Type/Ther.Class: 4S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION:
diclofenac sodium: nonsteroidal anti-inflammatory (NSAID)
misoprostol: antisecretory/mucoprotectant prostoglandin E_1

treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

DOSAGE FORM: tablet
STRENGTHS: 50 mg diclofenac sodium/ 200 µg misoprostol
75 mg diclofenac sodium/ 200 µg misoprostol

ROUTE OF ADMINISTRATION: oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1.

SUPPORTING DOCUMENTS:
See Chemistry Review #1.

RELATED DOCUMENTS (if applicable):
See Chemistry Review #1.

CONSULTS:

Division	Consult Date	Status	Comments
1. Division of Manufacturing and Product Quality HFD-324	02Feb96 14Jun96 (Compl)	**Acceptable**	has been withdrawn as manufacturer of the drug substance diclofenac sodium (see BC Amendment 27Jun96)
2. Division of Biometrics III	14Mar96	**Completed**	Expiration dating

HFD-720 (Dr. Milton Fan)	23Oct96(Compl)	two dosage strengths, 50/200 and 75/200, and six container-closures
3. Division of Pharmaceutical Evaluation II, HFD-870 (Dr. Lydia Kaus)	15Feb96	**Pending** Dissolution Spec proposal to perform dissolution on enteric coated
4. Labeling and Nomenclature Committee, HFD-530 (Dr. Dan Boring)	02Feb96 06May96(Let)	**Acceptable** ARTHROTEC was originally considered unacceptable due to similarity with AMPOTEC.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:
This application remains approvable (AE)

/S/ 9/10/97

George T. Chen, Ph.D.
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/10/97

Eric P. Duffy, Ph.D.
Supervisory Chemist, HFD-180

cc:
Orig. NDA 20-607
HFD-180/Division File
HFD-180/GChen
HFD-180/BStrongin
HFD-820/JGibbs
R/D Init by: Eduffy/9-4-97
GC/dob F/T 9-5-97/20607707.4GC

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-607 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 05Nov96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	22Dec95	26Dec95	16Jan96
AMENDMENT			
BC (Secifarma)	27Jun96	02Jul96	10Jul96
BZ (Stability)	23Feb96	26Feb96	05Mar96

NAME & ADDRESS OF APPLICANT:
G.D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

DRUG PRODUCT NAME
- Proprietary: Arthorotec™
- Nonproprietary/USAN: diclofenac sodium/misoprostol
- Code Name/#:
- Chem.Type/Ther.Class: 4S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION:
diclofenac sodium: nonsteroidal anti-inflamatory (NSAID)
misoprostol: antisecretory/mucoprotectant prostoglandin E_1

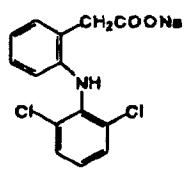
treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

DOSAGE FORM: tablet
STRENGTHS: 50 mg diclofenac sodium/200 µg misoprostol
75 mg diclofenac sodium/200 µg misoprostol
ROUTE OF ADMINISTRATION: oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Diclofenac sodium:
2-[2,6-dichlorophenyl)amino]benzeneacetic acid, mono sodium salt
$C_{14}H_{10}Cl_2NO_2Na$ MW 318.14

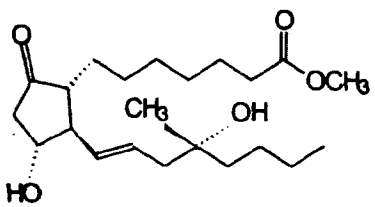
APPEARS THIS WAY
ON ORIGINAL

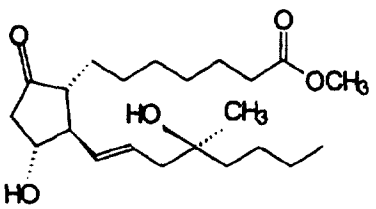
Misoprostol:
(±)methyl 11∝,16-



dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate
$C_{22}H_{38}O_5$ MW 382.54

APPEARS THIS WAY
ON ORIGINAL





SUPPORTING DOCUMENTS:

CONSULTS:

Division	Consult Date	Status	Comments
1. Division of Manufacturing and Product Quality HFD-324	02Feb96 14Jun96 (Compl)	**Acceptable**	has withdrawn as manufacturer of the drug substance diclofenac sodium (see BC Amendment 27Jun96)
2. Division of Biometrics III	14Mar96	**Completed**	Expiration dating

HFD-720 (Dr. Milton Fan)	23Oct96(Compl)	two dosage strengths, 50/200 and 75/200, and six container-closures
3. Division of Pharmaceutical Evaluation II, HFD-870 (Dr. Lydia Kaus)	15Feb96	**Pending** Dissolution Spec proposal to perform dissolution on enteric coated
4. Labeling and Nomenclature Committee, HFD-530 (Dr. Dan Boring)	02Feb96 06May96(Let)	**Acceptable** ARTHROTEC was originally considered unacceptable due to similarity with AMPOTEC.

REMARKS/COMMENTS:

This application is a combination of two approved drug products: Geigy Pharma's Voltaren (diclofenac sodium) Tablets, NDA 19-201, and Searle's Cytotec (misoprostol) Tablets, NDA 19-268.

The drug substance information is provided by reference to Searle's NDA 19-268 for the Misoprostol information,

The environmental assessment, provided in the Original Submission, Vol 1.8, 1.9, andf 1.10, is reviewed in Chemistry Review #2.

The BC Amendment of 27Jun96 withdraws as manufacturer of diclofenac sodium drug substance.

The BZ Amendment of 23Feb96 provides updated stability data out to one (1) year.

The application is not approvable in part because the following information is deficient:

Drug Product

Proposed master production record is not provided. The in-process controls is inadequate.

No sampling plan is provided for the regulatory specifications, references memorandum.

Regulatory specifications do not test drug release on intact DP for the diclofenac delayed release profile, biopharm consult. There is no impurity specification for diclofenac sodium.

Expiration date requested is 36 months based on 52 wk data.

CONCLUSIONS & RECOMMENDATIONS:

This application is not approvable.

cc:

Orig. NDA 20-607
HFD-180/Division File
HFD-180/GChen
HFD-181/BStrongin
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

filename: c:\wpfiles\chem\ng\20607607.lgc

12/4/96

/S/

George Chen, Ph.D.
Chemist, HFD-180

/S/

12/4/96

Eric P. Duffy, Ph.D.
Supervisory Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-607 **CHEM.REVIEW #:** 3 **REVIEW DATE:** February 13, 1997 MAR 5 1996

SUBMISSION TYPE	DOCUMENT	CDER	DATES ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL	22Dec95	26Dec95	16Jan96	05Nov96	1	05Dec96	IR
ORIGINAL [EA]	22Dec95	26Dec95	16Jan95	05Dec96	2	05Dec96	IR
AMENDMENT							
BC	27Jun96	02Jul96	10Jul96	05Nov96	1		
BZ	23Feb96	26Feb96	05Mar96	05Nov96	1		
BC (EA)	22Jan97	24Jan97	08Feb97	13Feb97	3		

NAME & ADDRESS OF APPLICANT:
G.D.Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

DRUG PRODUCT NAME
Proprietary: Arthrotec® Tablets
Nonproprietary/USAN: diclofenac sodium/misoprostol
Code Name/#:
Chem.Type/Ther.Class: 4S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION:
diclofenac sodium: nonsteroidal anti-inflammatory
misoprostol: antisecretory/mucoprotectant prostoglandin E$_1$
- treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

DOSAGE FORM: tablet
STRENGTHS: 50 mg diclofenac sodium/200 μg misoprostol
75 mg diclofenac sodium/200 μg misoprostol

ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1

SUPPORTING DOCUMENTS:
See Chemistry Review #1.

RELATED DOCUMENTS (if applicable):
See Chemistry Review #1.

CONSULTS: None

REMARKS/COMMENTS:
The Environmental Assessment review, see Chemistry Review #2, showed that the manufacture and patient use of Arthrotec Tablets meets the FDA's guidance criteria for Tier 0. Searle was requested to withdraw Items 7-11 from

Format 1 in the Teleconference of December 20, 1996. This BC Amendment, 22Jan97, contains the amended Environmental Assessment and the FOIA Environmental Assessment.

CONCLUSIONS & RECOMMENDATIONS:

The Environmental Assessment meets the requirements of FDA's Environmental Assessment Guidance. The FONSI may be issued.

3/5/97

George T. Chen, Ph.D.
Review Chemist, HFD-180

/S/ 3/5/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-607
HFD-180/Division File
HFD-180/CSO/BStrongin
HFD-180/GChen
R/D Init: Eduffy/2-28-97
GC/dob F/T 3-4-97/WP: c:\wpfiles\chem\N\20607702.3GC

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-607 **CHEM.REVIEW #:** 2 **REVIEW DATE:** December 5, 1996

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL [EA]	22Dec95	26Dec95	16Jan96

NAME & ADDRESS OF APPLICANT:
G.D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

DRUG PRODUCT NAME

Proprietary:	Arthorotec™
Nonproprietary/USAN:	diclofenac sodium/misoprostol
Code Name/#:	
Chem.Type/Ther.Class:	4S

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:
diclofenac sodium: nonsteroidal anti-inflamatory (NSAID)
misoprostol: antisecretory/mucoprotectant prostoglandin E_1

treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

DOSAGE FORM: tablet
STRENGTHS: 50 mg diclofenac sodium/200 µg misoprostol
75 mg diclofenac sodium/200 µg misoprostol

ROUTE OF ADMINISTRATION: oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1.

SUPPORTING DOCUMENTS:

CONSULTS:
See Chemistry Review #1.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:
Searle has shown that production of the drug product meets the requirements of Tier 0. All sites of drug substance and drug product manufacture have provided the required letters of self certification. Consistent with the current EA policy guidance, Searle has provided sufficient information to show that production of ARTHROTEC Tablets is in compliance with all applicable laws, permits, and consent orders. On this basis, a FONSI may be issued.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-607
HFD-180/Division File
HFD-180/GChen
HFD-180/BStrongin
R/D Init by: SUPERVISOR

filename: c:\wpfiles\ng\20607610.2gc

/S/ 12/16/96
George T. Chen, Ph.D.
Review Chemist, HFD-820

APPEARS THIS WAY
ON ORIGINAL

/S/ 12/16/96
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-820

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Brian Strongin	**Phone:** (301) 443-0483
Date: February 2, 1996	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Arthrotec	**NDA#** 20-607
Established name, including dosage form: diclofenac sodium/misoprostol tablets	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): Acute and chronic treatment for the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastric and/or duodenal ulcers.	
Initial Comments from the submitter (concerns, observations, etc.): No concerns at this time.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-607; HFD-180/division file; HFD-180/B.Strongin; HFD-180/G.Chen

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ARTHROTEC[R] (diclofenac sodium and misoprostol) Tablets

NDA 20-607

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTRO-INTESTINAL AND COAGULATION DRUG PRODUCTS (HFD-180)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-607
ARTHROTEC (diclofenac sodium/misoprostol) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **ARTHROTEC (diclofenac sodium and misoprostol) G.D. Searle & Co.** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Diclofenac sodium and misoprostol are synthetic drugs that will be administered orally in a combination tablet. The inner core of the tablet containing diclofenac sodium is for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and musculoskeletal disorders while the misoprostol outer core is a prophylactic treatment for preventing stomach ulcers associated with the diclofenac sodium drug substance. The drug substances are currently marketed in the United States in other products. The drug substances will be manufactured at facilities identified in the environmental assessment. The drug product will be manufactured by the applicant The finished drug product will be used in hospitals, clinics and homes throughout the United States.

Arthrotec may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is ppb. CDER has routinely found that concentrations ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA without format items 7, 8, 9, 10 and 11.

Disposal may result from waste generated during production, returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be

sent to licensed disposal facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

/S/

3/5/97
DATE

George T. Chen, Ph.D.
Review Chemist, HFD-180
Division of Gastrointestinal and
Coagulation Drug Products

/S/

3/5/97
DATE

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180
Division of Gastrointestinal and
Coagulation Drug Products

/S/

3/7/97
DATE

Nancy Sager
Environmental Assessment Team Leader
Center for Drug Evaluation and Research

Attachment:
Freedom of Information Copy (FOIA) of the Environmental Assessment for NDA 20-607.

cc:
NDA 20-607
HFD-180/Division File
HFD-180/EDuffy
HFD-820/JGibbs
HFD-357/NSager
HFD-181/BStrongin
HFD-180/GChen
R/D init: EDuffy/2-28-97
GC\dob **F/T** 3-4-97/WP: c:\wpfiles\chem\N\

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

PHARMACOLOGY REVIEW(S)

Strongin

M E M O R A N D U M

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

DATE: August 13, 1997 AUG 19 1997

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

SUBJECT: NDA 20,607 (Arthrotec) -
Amendment Dated June 18, 1997 -
Revised Draft Labeling

TO: NDA 20,607

In amendment dated June 18, 1997, the sponsor submitted a revised draft labeling. The portions of the draft labeling which relate to preclinical pharmacology and toxicology studies are evaluated and the appropriate recommendations are provided below.

1. PRECAUTIONS

a. Animal Toxicology

Evaluation: The display "ANIMAL TOXICOLOGY" gives the impression of a separate section from "PRECAUTIONS" section. The information under this caption pertains entirely to misoprostol. In the presently approved labeling for cytotec, it is shown as a subsection of "Animal Toxicology" under "PRECAUTIONS" section. The revised draft labeling should also use a similar format.

b. Carcinogenesis, Mutagenesis, Impairment of Fertility

Evaluation: The display "CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY" gives the impression of a separate section from "PRECAUTIONS". The revised draft labeling should adopt the standard caption for the subsection as "Carcinogenesis, Mutagenesis, Impairment of Fertility". There are several deficiencies in the contents of this subsection. They are:

(1) Information on ARTHROTEC is included as the last paragraph and it is also incomplete. This subsection should start with this information.

(2) Information from a teratology study in rabbits is misplaced in this subsection.

(3) The contents of the labeling are not in line with the currently used CDER wording.

(4) The quoted ratios between animal doses and recommended maximum human doses for diclofenac sodium and misoprostol are either inaccurate or not computed on a body surface area basis.

(5) Information for misoprostol mutagenic potential is incomplete.

(6) Information from teratological testing of misoprostol is misplaced in this subsection. All the above cited deficiencies should be corrected.

c. Pregnancy. Teratogenic Effects. Pregnancy Category-

Evaluation: This subsection is incomplete and inadequate. Animal teratology study results for arthrotec, diclofenac sodium and misoprostol are missing and they should be included.

Teratogenic Effects:

APPEARS THIS WAY
ON ORIGINAL

/S/ 8/19/97
Jasti B. Choudary, B.V.Sc., Ph.D.

Attachment: Marked Up Revised Draft Labeling

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Talarico

JBC/hw/8/15/97

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DRAFT LABELING

AUG - 9 1996

Reviewer: Gerald A. Young, Ph.D. Review # 1
Pharmacologist, HFD-180

Sponsor & Address: G.D. Searle & Co.
Skokie, IL 60077

Date of Submission: Original Submission - December 22, 1995
Amendment - February 5, 1996

Date of Receipt by HFD-180: Original Submission - December 28, 1995
Amendment - February 6, 1996

Date of Review: August 9, 1996

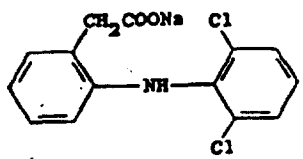
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUGS: ARTHROTEC® 50/ARTHROTEC® 75 tablets

Fixed combinations of diclofenac sodium and misoprostol

Drug (1): Diclofenac sodium (GP 45840)

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt/
[o-(2,6-dichloroanilino)phenyl] acetic acid sodium salt

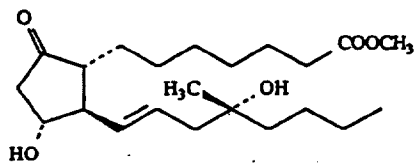


$C_{14}H_{10}Cl_2NNaO_2$ MW 318.13

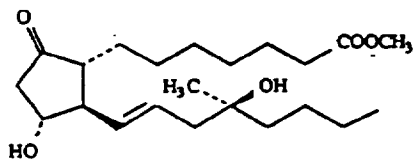
CATEGORY: Anti-inflammatory

Drug (2): Misoprostol (SC-29333)

(11α,13E)-(±)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester



(±)-S-form



(±)-R-form

$C_{22}H_{38}O_5$ MW 382.54

CATEGORY: Anti-ulcerative

FORMULATION: Enteric-coated core containing 50 mg (ARTHROTEC® 50) or 75 mg (ARTHROTEC® 75) of diclofenac sodium surrounded by an outer mantle containing 200 mcg of misoprostol. Formulation includes the inactive ingredients lactose, microcrystalline cellulose, starch (corn), povidone (polyvidone) K-30, magnesium stearate, methacrylic acid copolymer

sodium hydroxide, talc, triethyl citrate, crospovidone, colloidal silicon dioxide and hydrogenated castor oil.

PROPOSED MARKETING INDICATION: For acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastrointestinal ulcers.

DOSE: The highest recommended daily dose of ARTHROTEC® 50 would deliver 150 mg/day of diclofenac sodium and 600 mcg/day of misoprostol. The highest recommended daily dose of ARTHROTEC® 75 would deliver 150 mg/day of diclofenac and 400 mcg/day of misoprostol.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of study	Study/Report #	Drug Batch #	Page #
Pharmacology	----		4
Acute Oral Toxicity in the Mouse	PSA-87F-0331/0332	Misoprostol (M): 02800 Diclofenac (D): 57-B	6
Acute Oral Toxicity in the Rat	PSA-87F-0331/0332	M: 02800 D: 57-B	6
4-Week Oral Toxicity in the Rat	PSA-87F-0333	M: 01600 D: C0771	8
6-Month Oral Toxicity in the Rat	PSA-89F-0335	M: 02800 D: 57-B	10
4-Week Oral Toxicity in the Dog	PSA-87F-0334	M: 02800 D: 57-B	20
6-Month Oral Toxicity in the Monkey	PSA-98F-0336	M: 02800 D: 57-61A	24
MUTAGENICITY			
Ames Assay	PSA-89S-3556	M: 3D07510 D: 8935025	33
Forward Mutations in Chinese Hamster Ovary Cells	PSA-89S-3549	M: 3D07510 D: 8935025	34
Chromosomal Aberration Assay in Rat Lymphocytes	PSA-89S-3560	M: 3D07510 D: 8935025	35
Mouse Micronucleus Assay	PSA-89S-3558	M: 3D07510 D: 8935025	37
REPRODUCTIVE TOXICITY			
Segment II Oral Teratogenic Study in Rabbits	PSA-87S-3110	M: 01300 D: C0785	38

PHARMACOLOGY:

Primary Pharmacology

1. *In vivo* effects

Effects of diclofenac, misoprostol, and diclofenac:misoprostol combinations on phenylbenzoquinone-induced abdominal writhing in the mouse

Phenylbenzoquinone-induced (0.1 ml/10 g body weight, i.p.) abdominal writhing in mice was dose-dependently inhibited by either diclofenac (ED_{50} = 0.4 mg/kg; 1.0-10.0 mg/kg, p.o.) or misoprostol (ED_{50} = 2.0 mg/kg; 0.1-10.0 mg/kg, p.o.). The inhibitory effects of diclofenac:misoprostol combinations (0.1:0.1, 0.5:0.1, 0.1:0.3, and 0.1:1.0 mg/kg, p.o.) suggested synergism.

Effects of diclofenac, misoprostol, and diclofenac:misoprostol combinations on formalin-induced behavioral scores in the rat

Formalin-induced (intradermal administration of 0.1 ml of 2.5% formalin into the dorsal surface of one hindpaw) behavioral reactions were dose-dependently inhibited by diclofenac (-22.4%-66.2%, % of difference from control; 3-30 mg/kg, p.o.), but misoprostol (0.3 and 1.0 mg/kg, p.o.) had little or no inhibitory effect. In the case of the diclofenac:misoprostol combinations, inhibitory effects of lower doses of diclofenac (3 and 10 mg/kg, p.o.) seemed to be enhanced by misoprostol (1.0 mg/kg, p.o.), while inhibitory effects of a higher dose of diclofenac (30 mg/kg, p.o.) seemed to be decreased by misoprostol (0.3 and 1.0 mg/kg, p.o.). The reason for these interactions is not clear.

Effects of misoprostol on diclofenac-induced gastric ulcers in rats

Diclofenac (10 and 30 mg/kg, p.o.) produced dose-dependent increases in mean ulcer length/rat (2.0 and 32.2 mm) and mean number of lesions/rat (1.7 and 18.6). Co-administration of misoprostol (0.01-1.0 mg/kg) significantly inhibited diclofenac-induced (30 mg/kg, p.o.) mean ulcer length/rat and mean number of lesions/rat .

Effect of diclofenac, misoprostol, and diclofenac:misoprostol combinations on carrageenan-induced paw edema in the rat

Carrageenan-induced (subcutaneous administration of 0.25 mg in 0.1 ml of saline) rat paw edema in rats was inhibited by either diclofenac (ED_{40} = 1.84 mg/kg; 0.01-10.0 mg/kg, p.o.) or misoprostol (ED_{40} = 0.18 mg/kg; 0.003-0.3 mg/kg, p.o.). In the

case of diclofenac:misoprostol combinations, 0.01 and 0.03 mg/kg oral doses of misoprostol decreased the ED_{40}s of diclofenac (0.01-10.0, p.o.) to 0.04 and 0.36 mg/kg, respectively. When diclofenac (0.3-10 mg/kg, p.o.) was coadministered with oral misoprostol at diclofenac:misoprostol ratios of 100:1 and 10:1, there were no effects on the ED_{40}s of diclofenac. Thus, misoprostol either increased the efficacy of diclofenac-induced inhibition of carrageenan-induced paw edema or had no effect.

Prophylactic effect of diclofenac and diclofenac:misoprostol combinations in the rat adjuvant-induced arthritis model

Male rats were inoculated in the base of the tail with 2.0 mg of *M. butyricum* suspended in 0.05 ml of white paraffin oil. Beginning on the day of inoculation, rats were orally administered diclofenac (0.03, 0.1, 0.3 or 1.0 mg/kg/day), misoprostol (0.01, 0.03, 0.1 or 0.3 mg/kg/day) or diclofenac:misoprostol combinations of diclofenac (0.01, 0.03 or 0.3 mg/kg/day) with a fixed misoprostol dose of 0.3 mg/kg/day for 18 days. On Day 19, rats were sacrificed by CO_2 asphyxiation. In Experiment 1A, paw volume/body weight (PV/BW) ratios in the hydroxypropylmethylcellulose (HPMC) vehicle, distilled water and normal groups were 2.35, 2.82 and 1.5, respectively. Diclofenac (0.1-1.0 mg/kg, p.o.) dose-dependently reduced the mean PV/BW ratio (1.59-1.86) and increased the % reduction of PV/BW ratio (72.7-93.2%), while misoprostol (0.01-0.10 mg/kg, p.o.) had no significant effect on the mean PV/BW ratio and the % reduction of PV/BW ratio. In Experiment 1B, the PV/BW ratios in the HPMC vehicle, distilled water and normal groups were 2.30, 2.53 and 1.59, respectively. Diclofenac (0.03-0.3 mg/kg, p.o.) dose-dependently reduced the mean PV/BW ratio (1.64-1.87) and increased the % reduction of PV/BW ratio (70.2-94.7%), while misoprostol (0.03-0.3 mg/kg, p.o.) had no significant effect on the mean PV/BW ratio and the % reduction of PV/BW ratio. In Experiments 1A and 1B, there were no treatment-related effects on histopathology of ankle joints. In Experiment 2, the PV/BW ratios in the HPMC vehicle and normal groups were 2.26 and 1.49, respectively. Higher doses of diclofenac alone (0.1 and 0.3 mg/kg, p.o.) and diclofenac:misoprostol combination (0.3:0.3 mg/kg, p.o.) reduced the mean PV/BW ratio (1.62-1.99 and 1.80, respectively) and increased the % reduction of the PV/BW ratio (35.1-83.1% and 72.7%, respectively). There were no differences between diclofenac alone and diclofenac:misoprostol combination treatments. In Experiment 2, histopathology of the ankle joints was reduced by the 0.03 mg/kg dose of diclofenac alone, but not the 0.01 mg/kg dose. The histopathological effects of the diclofenac:misoprostol combination (0.01:0.3 mg/kg, p.o.) were not different from those produced by diclofenac alone (0.1 mg/kg, p.o.).

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

Finally, either diclofenac or misoprostol dose-dependently increased the number of mice in which phenylbenzoquinone-induced abdominal writhing was inhibited; inhibitory effects of diclofenac:misoprostol combinations suggested additivity. On the other hand, diclofenac dose-dependently inhibited formalin-induced behavioral scores in rats, while misoprostol had little or no effect; there was an unexplainable interaction between diclofenac and misoprostol on formalin-induced behavioral scores. Thus, interactive analgesic effects of diclofenac and misoprostol appear to be complex.

TOXICOLOGY:

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ACUTE TOXICITY:

1. Acute oral toxicity in the rat and mouse (Study No. PSA-87F-0331/0332)

This study was previously submitted as an Amendment to NDA 19-268 (3/11/88) and was previously reviewed (8/24/88). A copy of the review follows:

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The acute toxicity of diclofenac/misoprostol combination was conducted by Searle at France facility from Nov. 4-Dec. 5, 1986. Results of the studies is summarized below:

cies/strain	No./Sex	Body weight /age	Route	Dose range (mg/kg)	M : D	LD 50	Time to death(days)	Maximum non-lethal dose(mg/kg)	Toxic signs
se/CD-1	10		P.O.	Misoprostol(M)	20	> 20	-	> 20	(1)
				Diclofenac (D)	50	150(M)	10	100(M)	(2)
					100	150(F)	8	< 50(F)	
					150				
					225				
					300				
				"Low" Association	0.2 : 50	150(M)	5	50(M)	(3)
				Misoprostol/	0.4 : 100				
				Diclofenac	0.6 : 150	190(F)	6	100(F)	
				(ratio: 2/500)	0.9 : 225				
					1.2 : 300				
				"High" Association	0.27 : 50	150(M)	6	50(M)	(4)
				Misoprostol/	0.53 : 100				
				Diclofenac	0.8 : 150	190(F)	9	100(F)	
				(ratio: 2/375)	1.200 : 225				
					1.600 : 300				
t/CD	10		P.O.	Misoprostol (M)	20,000	> 20	-	> 20	(5)
				Diclofenac (D)	50	230(M)	8	100(M)	(6)
					100				
					150	100(F)	16	50(F)	
					300				
					600				
				"Low" Association	0.2 : 50	280(M)	28	150(M)	(7)
				Misoprostol/	0.4 : 100				
				Diclofenac	0.8 : 200	150(F)	7	50(F)	
				(ratio: 2/500)	1.2 : 300				
					2.4 : 600				
				"High" Association	0.26 : 50	240(M)	14	150(M)	(8)
				Misoprostol/	0.53 : 100				
				Diclofenac	1.07 : 200	110(F)	9	50(F)	
				(ratio: 2/375)	1.6 : 300				
					3.2 : 600				

1): Protration, reduced motor activity.
2), (3), (4): Reduced motor activity, prostration, convulsion.
5): loses stool, prostration, reduced motor activity.
6), (7), (8): loose stool, prostration, reduced motor activity, arch back/hair standing.

There were no significant differences between the LD50 values of the two combinations and the diclofenac alone except in female rats, where the LD50 values of the low combination was significantly higher than the LD 50 for diclofenac alone. In general, it was more toxic in female rats. In mice, no significant differences in the LD50 appeared, either among the two combinations and diclofenac, or between sexes.

Addendum to the Review:

The minimum oral lethal dose of misoprostol in male and female mice was not determined (>20 mg/kg). The minimum oral lethal dose of diclofenac was 50 mg/kg in males and females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:500 ratio) was 0.4:100 mg/kg in males and 0.8:200 mg/kg in females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:375 ratio) was 0.53:100 mg/kg in males and 1.07:200 mg/kg in females.

The minimum oral lethal dose of misoprostol in male and female rats was not determined (>20 mg/kg). The minimum oral lethal dose of diclofenac was 150 mg/kg in males and 100 mg/kg in females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:500 ratio) was 0.9:225 mg/kg in males and 0.4:50 mg/kg in females. The minimum oral lethal dose of the misoprostol:diclofenac combination (2:375 ratio) was 1.2:225 mg/kg in males and 0.27:50 mg/kg in females.

SUBACUTE/CHRONIC TOXICITY:

Rats

1. 4-Week Oral Toxicity of Diclofenac Sodium/Misoprostol (Study No. PSA-87F-0333)

This study was previously submitted as an Amendment to NDA 19-268 (3/11/88) and was previously reviewed (8/24/88). A copy of the review follows:

Four-Week Oral Toxicity Study of Misoprostol/Diclofenac in Rats

Testing laboratory: Searle at France facility

Date of the study: Jan-Feb., 1987

Animals: Charles River CD rats weighing 132-303 g and 40 days of age were used.

Methods: Six groups of rats each consisting of 10 males and 10 females were given orally vehicle (0.5% methylcellulose (w/v) and 0.1% polysorbate 80 in distilled water), low combination (misoprostol:diclofenac of 0.002:0.5 mg/kg), medium combination (0.008:2.0), high combination (0.024:6.0), low diclofenac (0.5 mg/kg) and high diclofenac (6.0 mg/kg) per day for 4 weeks. Lot numbers for misoprostol and diclofenac are 2800 and 578, respectively. Five other groups each consisting of 15 males and 15 females were tested for pharmacokinetics.

Results: There were no mortalities and toxic signs in the study.

Feces examiniation: Fecal samples were examined for the presence of blood (HEMOCCULT II test). There was a significant increase in the positive finding in animals treated with diclofenac alone, when compared to controls or to animals treated with the combination.

Body weight and food consumption: normal.

Clinical chemistry: A decrease in albumin concentration was observed in all treated females groups. This may be attributable to the higher plasma(3.5-6 times) concentration of diclofenac in females than in males.

Hematology and urinalysis: normal

Pharmacokinetics: Diclofenac concentrations were higher in females than in males. Dose proportionality was seen. There was evidence of dose accumulation. There was no pharmacokinetic difference between diclofenac alone and the combination except in males on day 24 where Cmax was three times higher in the declofenac alone group.

Gross pathology and organ weights: Normal.

Histopathology: Gastric lesions were observed in 9 of the 20 rats in the high dosage group of diclofenac alone. Atrophy/inflammation/fibrosis was seen in the pancrease of 4 animals in the high dosage groups of both diclofenac and the combination. Focal granulomas were noted in the livers of 3 of 10 females in the high dosage group of disclofenac alone.

In conclusion, comparison of diclofenac with diclofenac/misoprostol combination treatment did not reveal increased toxicity or any change in pharmacokinetics of diclofenac due to the addition of misoprostol. Dose selection was inadequate since high, medium, and low dosages only represents 1.5, 1/2 and 1/8 respectively, of the maximum human dose.

Addendum to the Review:

As shown in the following table for male rats, there were dose-related increases in C_{max} and AUC values for diclofenac and diclofenac:misoprostol combinations. T_{max} values were predominantly between 0.5 and 2.0 h. There were no significant differences in toxicokinetic parameters between diclofenac and diclofenac:misoprostol combinations.

Toxicokinetic parameters for orally administered diclofenac and diclofenac:misoprostol combinations in the male rat

Diclofenac and Diclofenac:Misoprostol Combinations (mg/kg, p.o.)	Day 1			Day 24		
	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)
0.5	0.13	1.0	0.28	0.36	0.50	0.54
6.0	0.85	0.50	2.92	3.33	0.50	5.78
0.002:0.5	0.17	1.00	0.49	0.29	2.00	0.86
0.008:2.0	0.49	0.50	1.05	0.28	1.00	0.90
0.024:6.0	0.81	2.00	3.42	0.61	7.00	3.32

As shown in the following table for female rats, there were dose-related increases in C_{max} and AUC values; there was no accumulation over 24 days. Plasma levels of diclofenac and diclofenac: misoprostol combinations were higher in females than males. The predominant T_{max} value was 0.50 h. There were no significant differences in toxicokinetic parameters between diclofenac and diclofenac:misoprostol combinations.

Toxicokinetic parameters for orally administered diclofenac and diclofenac:misoprostol combinations in the female rat

Diclofenac and Diclofenac:Misoprostol Combinations (mg/kg, p.o.)	Day 1			Day 24		
	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)
0.5	0.19	2.0	0.55	0.25	0.50	0.62
6.0	1.14	0.50	5.54	2.94	0.50	7.90
0.002:0.5	0.09	0.50	0.34	0.21	0.50	0.59
0.008:2.0	0.61	0.50	1.81	1.18	0.50	2.54
0.024:6.0	2.84	0.50	5.22	3.49	0.50	10.81

2. 6-Month Oral Toxicity of Diclofenac Sodium/Misoprostol (Study No. PSA-89F-0335)

This study was submitted as

Six-Month Oral Toxicity Study of the Combination of Misoprostol/Diclofenac in the Rat. (Report No. PSA-89F-0335)

Testing Laboratories: Searle Recherche et Développement, Valbonne, France

Study Started: March 31, 1987

Study Completed: February 9, 1989

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

Animals: Crl:CD(SD)Br; Males and females; Approximately 7 weeks of age; Weight; Males: 191-295 g, Females: 133-193 g

Drug Batch No.: Misoprostol: Lot No. 02800
Diclofenac: Lot No. 57B

Methods: The possible toxicological interaction of the combination of diclofenac and misoprostol versus diclofenac alone was evaluated in 26 week oral toxicity study in rats. Briefly, rats (20/sex/group) were orally (by gavage) administered Diclofenac alone at doses of 1, 2.5, and 6 mg/kg or in combination with misoprostol at doses of 4, 10 and 24 ug/kg, for 26 consecutive weeks. The dosage ratio of the combination (1 part misoprostol to 250 parts diclofenac) was chosen to mimic the likely clinical ratio. Misoprostol was administered as a dispersion which consisted of 1 part misoprostol and 100 parts hydroxypropyl methylcellulose, whereas, Diclofenac was dissolved in distilled water containing 0.5% methylcellulose 400 (w/v)and 0.1% polysorbate 80 (w/v). Diclofenac alone and the combination were administered in a total volume of 0.4 ml/kg. Animals in the control group (20/sex) received vehicles alone. An additional pharmacokinetic group (35 animals/sex/group) was used to determine the bioavailability of diclofenac and misoprostol. After 26 weeks of treatment 5 animals/group underwent a 4 week reversal period. Animals were observed at least 2X daily for signs of toxicity and/or mortality, with physical examinations conducted once at pretreatment, and weekly during the treatment period and reversal phase. Ophthalmologic examinations were performed at pretreatment and during weeks 13, 26, and 30 (recovery animals only). Body weights were recorded twice at pretreatment twice during the first 4 weeks and once weekly thereafter. Food consumption was determined once at pretreatment and weekly thereafter. Clinical chemistry and hematology was determined in plasma samples collected via the retro-orbital sinus from 10 animals/sex/group during weeks 8 and 17 and from all animals during weeks 25 and 31, with urinalysis conducted on samples from the same animals at the same time periods. Blood samples (approximately 1 ml) were also collected from 3 rats per

sampling time per sex per dosage group at 0, 0.25, 0.5, 1, and 6 hours after dosing on day 1, 95 and 179 and on days 1, 80, and 165 for determination of absorption and pharmacokinetics of diclofenac and misoprostol, respectively (each animal was bled only once for a given day). Following sacrifice, all animals in the main study group underwent gross pathologic examinations with determination of organ weights. Complete histological examinations were conducted on tissues from animals in the control, high dose combination and high dose diclofenac groups, and from all animals which did not survive to the scheduled sacrifice. Histological examinations of stomach, duodenum, jejunum, ileum, cecum, colon, and rectum were also conducted on all animals in remaining groups, along with any tissue which had gross lesions.

Results:

1. **Observed Effects:** Diclofenac-related clinical signs were observed in animals of the high dosage groups (diclofenac and combination) which were found dead or killed in extremis. These signs included: thin appearance, reduced motor activity, soiled urogenital area, pale extremities, labored breathing, and coldness to the touch.

2. **Mortality:** Treatment-related mortality included 3 females each in the high dose diclofenac and high dose combination groups. In addition, 1 male in the high dose diclofenac group and 1 female each in the high dose diclofenac and combination groups were sacrificed in extremis during weeks 22, 8, and 18. Other mortalities which resulted from apparent intubation errors included: 1 female control rat, 1 low dose combination male, 2 mid dose combination males, 1 high dose combination rat/sex.

3. **Body Weight/Food Consumption:** Diclofenac alone and in combination with misoprostol at the mid and high doses produced small reductions in body weight gains over the 26 week treatment period (Day 1 through Day 179). Mean body weight gains were reduced in mid and high dose diclofenac groups by 7.43 and 14.18% in males and by 6.5 and 12.34% in females, respectively. Similar reductions in mean body weight gains of 24.89 and 10.69% in males and of 7.78 and 2.57% in females were observed in rats in the mid and high dose combination groups. There were no apparent treatment-related changes in food consumption in any groups tested.

4. **Hematology:** At week 25, females exhibited dose-dependent increased neutrophils (95 and 507%, and 49 and 549% in mid and high dose diclofenac and mid and high dose combination groups, respectively; from a mean control value of 0.88 x 10^9 cells/L). Increased neutrophils resulted in significant increases in white blood cells (WBC) in the high dose diclofenac (77%) and high dose combination groups (91% from a control value of 8.2 x 10^9 cells/L). High dose females (diclofenac and combination) also

exhibited significant increases absolute monocytes (206 and 223%) and eosinophils (300 and 154%) compared to control values of 0.31 x 10^9/L and 0.11 x 10^9/L, respectively. Small, but significant decreases in red blood cells (RBCs, 11%), hemoglobin (Hb, 15%) and hematocrit (Hct, 12%) were observed in high dose combination females, while high dose diclofenac females only showed decreased hemoglobin (6.38%). Females in the high dose diclofenac and combination groups also exhibited increased platelets (24 and 37% over a mean value for control females of 901 x 10^9 platelets/L) which resulted in a slight decrease in prothrombin times (8.9%) compared to a control value of 10.1 seconds. In general hematological effects were not evident in rats by the end of the reversal period, with the exception of WBCs and neutrophils which remained elevated (117% and 319%) in high dose combination females at the end of the reversal period (reversal week 5) compared to mean control values of 7.6 x 10^9 WBCs/L and 1.35 x 10^9 neutrophils/L, respectively.

5. Blood Chemistry: Treatment-related changes in blood chemistry included decreased total protein in females of both the high dose diclofenac and the high dose combination groups , which was due mainly to decreased albumin concentrations in these groups and in the high dose diclofenac and high dose combination groups, respectively).. The decreased albumin concentrations in females also resulted in reduced A/G ratios during week 24 in these same groups (11% and 22%) in the high dose diclofenac and high dose combination groups, respectively. The aforementioned reductions in total protein, albumin and A/G ratios persisted through the recovery period. Other significant changes in biochemical parameters included: 1) increased aspartate aminotransferase levels in: mid dose diclofenac males (60.78 and 35.4%; weeks 17 and 24) and in high dose combination group (328.84%, recovery week 5); 2) increased alanine aminotransferase in mid dose diclofenac males (90 and 42%; weeks 17 and 24) and in high dose diclofenac females (275% during recovery week 5); 3) increased alkaline phosphatase in high dose diclofenac and combination females (11 and 22% , respectively, during week 24) and in all treatment groups, except low and mid dose combination females, during week 5 of the recovery period (%; not dose related).

6. Urinalysis: No treatment-related changes were observed in urinalysis.

7. Ophthalmologic Examinations: Ophthalmoscopic observations included the following: hyper-reflectivity of the retina (one female in the high dose combination group); 5 cases of retinal hemorrhage (animals of both sexes across all treatment groups), sporadic incidence of corneal opacity, superficial keratitis (associated in 2 cases with edema or dystrophy) and absence of identifiable ocular structures (a few animals in all dose groups) and finally, three cases of capsular or incipient cataracts of the posterior part of the lens were observed across the control and low dose combination groups. In all cases ophthalmologic observations appeared sporadically or possibly related to trauma or infection (presumably due to blood collection) and did not appear treatment-related.

8. Organ Weights: Treatment-related changes in organ weights included: increased absolute and relative weights for liver in females from the high dose combination group (increases of 17,19 and 17% for absolute liver weights and liver/body and liver/brain weight ratios, respectively) and increased absolute and relative weights for spleen in females from both the high dose diclofenac group (increases of 30.4, 38.5, and 25.2% for absolute spleen weights and spleen/body and spleen/brain weight ratios, respectively) and the high dose combination group (increases of 64, 69 and 64% for absolute spleen weights and spleen/body and spleen/brain weight ratios, respectively). The aforementioned changes in liver and spleen weights persisted to a similar degree at the end of the recovery period (recovery week 5) with no evidence of reversibility.

9. Gross Pathology: Four females from each high dosage group (High dose Combination [HC] and High dose Diclofenac [HD]) and one male from the HD group which died or were killed in extremis exhibited gross lesions in the abdominal and/or thoracic cavities which included: abdominal cavity peritonitis (3 females each in the HC and HD groups); adhesion of various organs including heart (1 HD female), lungs (1 HC male), intestines (2 HC females) and liver (1 of 5 HC females); edema of the viscera (1 HC female); ulcerations of the jejunum (2 HD females) and small intestines (1 female each in the HC and HD groups); enlarged spleen (1 HD female) and mucosal hyperemia of the stomach (1 HD female) red discoloration of the pancreas (1 HD female) and discoloration of the thymus (1 male each in the mid dose combination group and in the HC). Treatment-related gross pathological findings in animals which survived to the scheduled sacrifice are presented in Table 1 (succeeding page).

Table 1. Gross Pathological Findings in Rats Following Six months of Oral Administration of Vehicle, Diclofenac or the Combination of Diclofenac/Misoprostol.

	Males							Females						
Group	CT	LC	MC	HC	LD	MD	HD	CT	LC	MC	HC	LD	MD	HD
No. of Animals	15	14	13	14	15	15	14	14	15	15	11	15	15	12
Gross Observation:														
Jejunum														
Dilated/thickened...	0	0	0	0	0	0	0	0	0	0	3	0	0	1
Thickening.....	0	0	0	0	0	0	1	0	0	0	1	0	0	4
Hyperemia.....	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Nodule.....	0	0	0	0	0	0	0	0	0	0	3	0	0	0
Mesenteric lymph node														
Enlarged.....	0	0	0	0	0	0	0	0	0	0	3	0	0	1
Submaxillary lymph node, Enlarged.....	0	2	0	1	1	0	1	0	0	0	0	0	0	0
Enlarged Spleen.....	0	0	0	0	0	0	0	0	0	1	1	0	0	1
Stomach														
Mucosal hyperemia...	0	0	0	1	0	1	1	0	0	0	0	0	0	0
Thickened wall.....	0	0	0	1	0	0	1	0	0	0	0	0	0	0
Dark spot.....	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Thymus														
Enlarged.....	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Small petechial Hemorrhages.....	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Uterus														
Dilated/thickened...	----------							0	2	1	2	1	1	0

CT = Vehicle control;
LC = Low dose Diclofenac/misoprostol [4 ug/kg: 1 mg/kg]
MC = Mid dose Diclofenac/misoprostol [10 ug/kg:2.5 mg/kg]
HC = High dose diclofenac/misoprostol [24 ug/kg:6 mg/kg]
LD = Low dose Diclofenac [1 mg/kg]
MD = Mid dose Diclofenac [2.5 mg/kg]
HD = High dose Diclofenac [6 mg/kg]

Briefly, the data in Table 1 show that High dose Combination (HC, Misoprostol/Diclofenac) and High dose Diclofenac (HD) treatments produced nodules, dilation and/or thickening in the jejunum (5

females and 1 male from the HD group and 7 females from the HC group). Other gross lesions included: enlarged spleens (1 female each, in the HC and HD groups and 1 female in the Mid dose Combination group [MC]); enlarged mesenteric lymph nodes (3 HC females and 1 HD female); hyperemia of the jejunum (1 HD male and 1 Mid dose Diclofenac [MD] female); mucosal hyperemia of the stomach (1 male each, in the HC, HD and MD groups); thickened stomach wall (1 HC male); dark spot in the stomach (1 HD male and 1 Low dose Combination [LC] female); enlarged thymus (1 HC male) and petechial hemorrhages in the thymus (1 HD male). Females in both treatment groups (diclofenac and combination) also exhibited an increased incidence of dilated/thickened uterus. However, this latter finding was not dose dependent and its relationship to treatment is unknown. Gross observations in rats at the end of the recovery period included: jejunal dilation/thickening (2 of the 4 HC females); jejunal hyperemia 1 of 4 HC females); abdominal cavity adherence (1 of 4 HC females); enlarged spleen (1 of 4 HC females), liver nodule (1 of 5 HD males) and enlarged submaxillary lymph nodes (1 male each in the low and high dose combination and low and high dose diclofenac groups). Uterine dilation was also observed in 1 of 5 and 2 of 5 females in the LC and MC groups. Finally, stomach mucosal hyperemia was seen in 1 of 5 Low dose Diclofenac (LD) females the at the end of the reversal period.

10. Histopathology: The incidence of treatment-related histological observations in rats which survived to the scheduled sacrifice is presented in Table 2 (succeeding pages). Briefly, these data show that diclofenac and the combination of diclofenac/misoprostol produced ulcerations in: the glandular mucosa of the stomach (1 MD and 3 HD males and in 1 female each in the LC and HC groups); the mucosa of the jejunum, mostly accompanied by a parietal granulation (7 HC females and 1 male and 6 females from the HD groups) and the mucosa of the cecum (1 female each in the HD and HC groups). Additional treatment-related findings included: extramedullary hematopoiesis of the spleen (5 HC females and 1 HD female); peritonitis of the jejunum (1 HC female); increased incidence of adenitis of the sub-maxillary and mesenteric lymph nodes (females in both high dose groups), with plasma cell infiltration of the sub-maxillary lymph node (3 HD males) and sinusal edema/cystic spaces in the mesenteric lymph nodes (5 HC females and 4 HD females). Finally, acute hemorrhage of the thymus and loss of thymic cortical lymphocytes was also observed in 1 HD male and in 1 HC male, respectively. Other possible treatment-related effects include a slight increased incidence of hepatic vacuolation (HD males and females), necrosis (1 male and 1 female in the HD and HC groups, respectively), and non-suppurative hepatitis (males in both the HC and HD groups). Finally, a low incidence of uterine luminal distension was observed in 1 to 3 females in all treatment groups (combination and diclofenac) versus none in the control group.

Table 2. Histopathological Findings in Rats Following Six months of Oral Administration of Vehicle, the Combination of Diclofenac/Misoprostol or Diclofenac alone.

	Males							Females						
Group	CT	LC	MC	HC	LD	MD	HD	CT	LC	MC	HC	LD	MD	HD
No. examined*	15	14	13	14	15	15	14	14	15	15	11	15	15	12
Microscopic Findings:														
Stomach														
Glandular Mucosa ulceration.....	0	0	0	0	0	1	3	0	1	0	1	0	1	1
Spleen														
Extramedullary hematopoiesis.....	0	-	-	0	-	-	0	0	-	-	5	-	-	1
Jejunum														
Mucosal ulceration...	0	0	0	0	0	0	1	0	0	0	7	0	0	6
Parietal granulation.	0	0	0	0	0	0	0	0	0	0	7	0	0	6
Mucosal hyperemia....	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Peritonitis.....	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Cecum														
Mucosal ulceration...	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Colon														
Lymphoid hyperplasia.	0	2	3	3	4	1	0	1	4	1	0	3	3	1
Heart														
Chronic myocarditis..	2	-	-	4	-	-	3	1	-	-	0	-	-	0
Myocardial necrosis..	0	-	-	1	-	-	2	0	-	-	0	-	-	0
Liver														
Hepatocytic vacuolation.....	4	-	-	2	-	-	7	4	-	-	5	-	-	6
Necrosis.....	0	-	-	1	-	-	0	0	-	-	0	-	-	1
Non-suppurative hepatitis.....	3	-	-	8	-	-	8	9	-	-	10	-	-	4
Submaxillary LN														
Adenitis.....	4	2	-	2	1	-	2	3	-	-	6	-	-	6
Plasma cell infiltration.....	0	-	-	0	-	-	3	1	-	-	0	-	-	0

- = No animals examined
CT = Vehicle control
LC = Low dose Diclofenac/misoprostol [1 mg/kg:4 ug/kg]
MC = Mid dose Diclofenac/misoprostol [2.5 mg/kg:10 ug/kg]
HC = High dose diclofenac/misoprostol [6 mg/kg:24 ug/kg]
LD = Low dose Diclofenac [1 mg/kg]
MD = Mid dose Diclofenac [2.5 mg/kg]
HD = High dose Diclofenac [6 mg/kg]

Table 2. (Cont...)

Cont...	Males							Females						
Group No.	CT	LC	MC	HC	LD	MD	HD	CT	LC	MC	HC	LD	MD	HD
No. examined	15	0	0	14	0	0	14	14	2	1	11	0	1	12
Microscopic Findings:														
Mesenteric LN														
Adenitis.....	0	-	-	0	-	-	1	0	-	-	4	-	-	6
Sinusal edema/cystic spaces.....	0	-	-	0	-	-	0	0	-	-	5	-	-	4
Thymus														
Acute congestion/ hemorrhage.....	0	-	-	0	-	-	1	0	-	-	0	-	-	0
Loss of Cortical lymphocytes.....	0	-	-	1	-	-	0	0	-	-	0	-	-	0
Uterus														
Luminal distension..	-	-	-	-	-	-	-	0	2	1	3	-	1	3

- = No animals examined
CT = Vehicle control
LC = Low dose Diclofenac/misoprostol [1 mg/kg:4 ug/kg]
MC = Mid dose Diclofenac/misoprostol [2.5 mg/kg:10 ug/kg]
HC = High dose diclofenac/misoprostol [6 mg/kg:24 ug/kg]
LD = Low dose Diclofenac [1 mg/kg]
MD = Mid dose Diclofenac [2.5 mg/kg]
HD = High dose Diclofenac [6 mg/kg]

Histological findings in animals which were sacrificed at the end of the recovery period were limited ulcerations with parietal granulations (2 of 4 HC females). The four females from each of the high dose groups and the one male from the high dose diclofenac group which died or were killed in extremis exhibited similar, but more severe histological lesions including: erosions/ulcers of the forestomach, glandular mucosa, jejunum, ileum, Cecum and rectum; diffuse peritonitis in multiple organs including, stomach, spleen, pancreas, duodenum, jejunum, ileum, cecum, colon, liver, ovaries, urinary bladder and mesenteric lymph node; pericarditis (1 HD female); acute gastritis (1 HD female); extramedullary hematopoiesis in the spleen; cortical hypertrophy of the adrenal glands (2 females each in the HD and HC groups); adenitis and plasma cell infiltration of the submaxillary lymph node, adenitis and sinusoidal edema/cystic spaces of the mesenteric lymph node and acute congestion/ hemorrhage of the thymus with loss of cortical lymphocytes.

11. Plasma Concentrations: Diclofenac and the combination of diclofenac and misoprostol were rapidly absorbed following oral dosing with maximal plasma levels of diclofenac attained between 0.25 and 1.0 hr in all dose groups. A summary of the Cmax and AUC values for diclofenac on days 1, 95 (week 14) and 179 (week 26) is presented in Table 3, (below).

Table 3. Cmax and AUC values for Diclofenac in Rats Following Oral Administration of Diclofenac Alone or in combination with misoprostol on Days 1, 95, and 179.

Group #	Sex	Cmax (ug/ml)			AUC (ug·hr/ml)		
		Day 1	Day 95	Day 179	Day 1	Day 95	Day 179
Control	M	0.00	0.00	0.00	0.00	0.00	0.00
LD	M	0.18	0.31	0.44	0.62	1.68	0.62
MD	M	0.52	1.14	1.01	2.13	3.57	3.29
HD	M	1.32	3.60	2.90	4.16	6.50	10.96
LC	M	0.23	0.30	0.33	0.20	0.77	1.07
MC	M	0.56	0.70	1.50	2.04	1.63	2.05
HC	M	1.24	1.95	1.67	4.31	6.66	3.65
Control	F	0.00	0.00	0.00	0.00	0.00	0.00
LD	F	0.28	0.85	0.86	1.01	1.99	2.03
MD	F	0.85	2.01	3.82	1.48	2.62	5.05
HD	F	5.24	3.13	4.13	8.25	8.83	14.52
LC	F	0.29	0.78	1.32	0.85	2.34	2.98
MC	F	1.54	1.09	1.71	2.05	4.42	5.07
HC	F	1.89	5.02	2.73	5.34	8.60	8.89

Control = Vehicle controls ;
LD = Low dose Diclofenac [1 mg/kg]
MD = Mid dose Diclofenac [2.5 mg/kg];
HD = High dose Diclofenac [6 mg/kg];
LC = Low dose Diclofenac/misoprostol [1 mg/kg:4 ug/kg]
MC = Mid dose Diclofenac/misoprostol [2.5 mg/kg:10 ug/kg]
HC = High dose diclofenac/misoprostol [6 mg/kg:24 ug/kg]

Briefly,these data show that increasing doses of Diclofenac (alone or in combination with misoprostol) produced variable, but linear increases in Cmax and AUC values which were generally dose proportional in both sexes. Overall, Cmax and AUC values were increased in females compared to males and were generally greater on Day 179 compared to Day 1. However, misoprostol did not interfere with the pharmacokinetics of diclofenac at the doses tested herein, with the possible exception of male rats on day 179, where mean AUC values were higher after administration of diclofenac alone (AUC = 10.96 $\pm$ 2.85 μg.hr/ml) compared to the combination (AUC = 3.7 $\pm$ 0.29 μg.hr/ml). However, since such

differences were not observed in any other dose groups or time points, this difference could be due to intergroup variability.

Plasma concentration data on SC-30695, the main metabolite of misoprostol (day 80 [week 12] and day 165 [week 24], data not shown), only demonstrated that misoprostol was well absorbed on days 80 and 165 in the high dose combination group, as analytical problems and instability of SC-30695 precluded further assessments.

In conclusion, 6-month oral administration of misoprostol at doses of 4, 10, and 24 ug/kg had no apparent effect on the toxicity profile of diclofenac (coadministered orally, at respective doses of 1, 2.5 and 6 mg/day) in rats, compared to the toxicity profile of diclofenac alone. Diclofenac alone or in combination with misoprostol produced clinical signs of thin appearance, reduced motor activity, soiled urogenital area, pale extremities labored breathing, coldness to touch and death in high dose rats. Mild reductions in body weight gains, alterations in hematology, clinical chemistry and increased organ weights for spleen and/or liver compared to control values were also observed in mid and high dose rats of both treatment groups. Target organs of toxicity included: 1) organs of the GI tract (stomach jejunum, cecum, and colon); 2) spleen (enlarged with extramedullary hematopoiesis); 3) Lymph nodes (enlarged with adenitis, sinusoidal edema and plasma cell infiltration; and 4) thymus, with increased incidence of congestion/hemorrhage and loss of cortical lymphocytes. In general, gross and histological signs were most prevalent in both high dose groups, and were more severe in females compared to males. Females also had higher diclofenac plasma concentrations compared to their male counterparts. However, coadministration of misoprostol had minimal effects on the absorption or pharmacokinetics of orally administered diclofenac in rats. The no effect oral dose for the combination of misoprostol and diclofenac in rats (at a dose ratio of 1:250) was 4 µg/kg and 1 mg/kg, respectively.

Dogs

1. 4-Week Oral Toxicity of Diclofenac Sodium/Misoprostol (Study No. PSA-87F-0334)

This study was previously submitted as an Amendment to NDA 19-268 (3/11/88) and was previously reviewed (8/24/88). A copy of the review follows:

Four Week Oral Toxicity Study of Diclofenac/Misoprostol in Dogs

Testing Laboratory: Searle in France

Date of the study: Dec 16, 1986 to Jan 16, 1987.

GLP requirement: A statement of compliance with GLP regulation was included.

Animals: Beagle dogs weighing and about 6-8 months of age were used.

Methods: Six groups of animals each consisting of 4 males and 4 females were given control (empty capsules), low diclofenac (0.5 mg/kg/day), high diclofenac (2 mg/kg/day), low combination (misoprostol:diclofenac of 0.002:0.5 mg/kg/day), medium combination (0.004:1) and high combination (0.008:2 mg/kg/day) by capsule for 4 weeks.

Results:

Mortality: One male the high dosage diclofenac group was found dead on day 17. Two males and one female of the high dosage combination were found dead between days 20 to 25. All remaining surviving dogs in these two groups were sacrificed on day 25 due to the mortality level and the general poor condition.

Clinical signs: Dark feces, red tinged in feces, bloody feces, loose stools and emesis, reduced motor activity, salivation, pallor of mucosa, and thinness of body were observed in all drug-treated groups.

Body weight: There were marked body weight decreases in the high diclofenac and high combination groups in the study. However, there were no differences in body weight changes from study day 1 among all dosage groups.

Food consumption: Food consumption was reduced more frequently in animals of the two high dosage groups.

EKG: None of the changes were considered to be drug-related.

Clinical chemistry: Dose-related decreases of protein , and albumin (20-50%) concentrations were observed in all treated groups except in females of the low combination group. Calcium concentration was decreased A decrease of alanine aminotransferase activity was observed. There was a decrease in alkaline phosphatase. Decreases of sodium concentration (7%) was observed in high diclofenac group. Choride concentration was normal.Triglyceride concentration was increased in the high dosage groups and the medium dosage group.Creatinine concentration was increased (8%) in high diclofenac group. There were no significant differences in the above-mentioned parameters between diclofenac alone and combination groups.

Hematology: There was a dose dependent decrease of red blood cell count), hematocrit ', and hemoglobin in the high dosage groups and medium dosage group. Mean corpuscular hemoglobin and volume was decreased (10%) in the high dosage groups. White blood cell count were markedly increased in all dosage groups. There was an increase in percentage of neutrophils with a concomitant decrease in percentage of lymphocytes in all treated groups. In general, the above-mentioned parameters were not enhanced by addition of misoprostol.

Urinalysis: Normal except some contamination of urine by blood from feces was observed.

Bioavilability: Plasma diclofenac concentrations were lower in males. No pharmacokinetic difference was observed after the administration of diclofenac alone or in combination with misoprostol.

Organ weights: Spleen weights were dose-dependently increased at all doses (50-170%) and more pronounced in males than in females. Thymus weights were decreased (67%) in animals at the high dosage of diclofenac alone and in combination with misoprostol. Kidney weight increased dose dependently in all treated groups, but they were not statistically significant. Lower prostate , testis, and epididymis weights were observed in a few animals treated with the combination of misoprostol and diclofenac (2 out of 4 at the low, 1 out of 4 at the medium and 2 out of 4 at the high dosage group). Again, the differences were not statistically significant.

Gross pathology: Ulcerations in GI tracts were found in animals of the high dosage groups and medium combination group. In the kidney, white or red discoloration of the papilla was observed in animals of high dosage groups. The prostate was reduced in size in 2 (sponsor stated 3, instead) out of 4 animals of high dosage combination group.

Histopathology: Ulceration or erosions were observed in GI tracts in animals of all treatment groups except in males of both the low dosage of diclofenac alone and the combination. Other major histopathological findings are summarized below:

	Male						Female					
Groups *	1	2	3	4	5	6	1	2	3	4	5	6
No. examined	4	4	4	4	4	4	4	4	4	4	4	4
Kidney												
papilary edema	0	0	1	1	3	4	0	1	2	0	2	2
papillary necrosis	0	0	2	0	0	0	0	0	1	0	0	1
Spleen												
Extramedullary hematopoisis	0	1	3	0	0	2	0	1	3	0	3	2
Thymus atrophy	0	0	2	0	1	2	0	0	2	0	0	2
Prostate hypoplasia	0	0	0	2	1	3						
Testis												
Oligospermia	0	0	0	1	1	3						
Epididymis												
no spermatozoa	0	1	0	1	1	2						

* 1: control, 2: low diclofenac, 3: high diclofenac
4: low combination, 5: medium combination, 6: high combination

The data indicated that prostate hypoplasia, oligospermia in testis, no spermatozoa in epididymis, and papillary edema in kidneys were observed dose-dependently in the males of all combination groups. Thus, renal toxicity and lethality due to diclofenac were somewhat enhanced by addition of misoprostol at dose equavalent to 1/2 of the recommended maximum human dose and combination of two compounds might induce toxicities in male reproductive organs. Applicant mentioned that the reproductive toxicity may be attributable to vriable matuiry of the organs due to animal's age (6-8 months). Again, this study did not provide safety margin of the combination. Dose selection was inadequate since high dose only represents 1/2 of the maximum human dose. However, there appears to be limiting toxicity i.e., mortality with high dose.

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Addendum to the Review:

As shown in the following table for male dogs, there were dose-related increases in AUC values; C_{max} values were more variable. T_{max} values varied between 1 to 4 h. There were no significant differences in toxicokinetic parameters between diclofenac and diclofenac:misoprostol combinations.

Toxicokinetic parameters for orally administered diclofenac and diclofenac:misoprostol combinations in the male dog

Diclofenac and Diclofenac:Misoprostol Combinations (mg/kg, p.o.)	Day 1			Week 4		
	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)
0.5	1.58	1.13	4.94	1.80	0.63	3.91
2.0	6.32	1.00	15.69	1.79	2.33	6.44
0.002:0.5	0.92	3.25	3.25	1.68	2.50	4.42
0.004:1.0	2.94	1.63	6.67	2.08	1.88	6.10
0.008:2.0	4.46	1.75	14.72	1.23	4.00	6.23

As shown in the following table for female dogs, there were dose-related increases in AUC values; C_{max} values were more variable. T_{max} values varied between 0.25 to 3.5 h. There were no differences between males and females. There were no significant differences in toxicokinetic parameters between diclofenac and diclofenac:misoprostol combinations.

Toxicokinetic parameters for orally administered diclofenac and diclofenac:misoprostol combinations in the female dog

Diclofenac and Diclofenac:Misoprostol Combinations (mg/kg, p.o.)	Day 1			Week 4		
	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)
0.5	1.94	0.25	5.28	1.69	2.13	4.11
2.0	5.48	2.38	14.78	4.83	1.38	16.16
0.002:0.5	1.46	0.88	3.78	0.91	3.38	3.00
0.004:1.0	3.75	0.63	9.39	3.03	1.88	6.23
0.008:2.0	5.65	2.75	16.22	6.31	0.63	16.63

Monkeys

1. 6-Month oral toxicity of Diclofenac Sodium/Misoprostol (Study No. PSA-89F-0336)

This study was previously submitted as A copy of the review follows:

Six-Month Oral Toxicity Study of the Combination of Misoprostol/Diclofenac in the Cynomolgus Monkey. (Report No. PSA-89F-0335)

Testing Laboratories: Searle Recherche et Développement, Valbonne, France

Study Started: June 9, 1987

Study Completed: March 13, 1989

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

Animals: Cynomolgus Monkeys; Age not indicated; Weight; Males: 2.5-3.8 kg, Females: 2.2-3.5 kg

Drug Batch Nos.: Misoprostol: Lot No. 02800
Diclofenac: Lot No. 57-61A

Methods: The possible toxicological interaction of the combination of diclofenac and misoprostol versus diclofenac alone was evaluated in 26 week oral toxicity study in monkeys. Briefly, monkeys (6/sex/group) were orally administered (by nasogastric route) diclofenac alone at doses of 6, and 50 mg/kg or at doses of 6, 17, and 50 mg/kg in combination with misoprostol at respective doses of 24, 68, and 200 ug/kg for a period of 6 months. The basis of dose selection was not indicated. Diclofenac was dissolved in distilled water and misoprostol was dispersed in hydroxypropyl methylcellulose, HPMC (1 part misoprostol:100 parts HPMC) and administered in a volume of 3 ml each. The diclofenac alone group received an additional 3 ml/kg distilled water. Control animals (6/sex) received 6 ml/kg distilled water. After 26 weeks of treatment, 2 animals/group (except for high dose diclofenac females, where only one animal was selected) underwent a 4 week reversal period. Animals were observed prior to and approximately 2-3 hours post dosing for signs of toxicity and/or mortality, with physical examinations conducted once at pretreatment, during weeks 7, 14, and 24 of the treatment phase and during and during week 4 of the reversal period. Ophthalmologic examinations were performed on anesthetized animals once at pretreatment, during week 24 of treatment and during week 3 of the reversal phase. Body weights were recorded once at pretreatment, once one week before the first day of treatment for selected animals, on day 4 of the study and every 2 weeks thereafter. Measurements of food and water consumption were not indicated. Serial venous blood samples (8 ml total) were collected from all animals including controls on days 1, 85 (week 13) and 176 (week 26) for determinations of diclofenac and SC-30695 (primary metabolite of misoprostol) concentrations. Additional venous blood samples (2.5 ml) were collected at pretreatment, and before dosing during weeks 4, 8, 14, 18, and 25 and at the end of the reversal period for analysis of clinical chemistry and hematology. Urinalysis was not indicated. Electrocardiographic examinations were performed on anesthetized animals at pretreatment, after treatment during weeks 14 and 24 and during week 4 of the recovery period. Complete gross and histological examinations were performed on all animals which died or were killed in extremis and at the scheduled sacrifice.

Results:

1. **Observed Effects:** Monkeys found dead or killed in extremis exhibited clinical signs of toxicity which included reduced motor activity, prostration, hypothermia, paleness of mucosae, edema and redness of eyelids swelling and wounds of the skin. Treatment- related clinical signs in surviving animals included: loose stools (males in the mid and high dose combination groups and females mainly in the high dose combination group); salivation before treatment (mid and high dose combination males and high dose combination females); and a dose-related increased incidence of small exudative wounds, primarily located on the