

**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

	<u>DOCUMENT</u>	<u>CDER</u>	<u>ASSIGNED</u>	<u>REVIEW</u>	<u>NUM LET ST</u>
ORIG. AMENDMENTS	22Dec95	26Dec95	16Jan96		1
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-inflammatory (NSAID)  
misoprostol: antisecretory/mucoprotectant prostaglandin E<sub>1</sub>  
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:  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.

<u>Division</u>	<u>Consult Date</u>	<u>Status</u>	<u>Comments</u>
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 Division of Manufacturing and Product Quality HFD-324	02Feb96 14Jun96 (Compl)	Acceptable	has withdrawn as manufacturer of the drug substance diclofenac sodium (see BC Amendment 27Jun96)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  (Dr. Dan Boring)	02Feb96 06May96 (Let)	Acceptable	ARTHROTEC was originally considered unacceptable dur to similarity with AMPOTEC.

**REMARKS/COMMENTS:**

Searle is responding to the "approvable" action letter of 17Sep97.

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA may be approved (AP).

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*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

<u>SUBMISSION TYPE</u>		<u>DOCUMENT</u>	<u>CDER</u>	<u>ASSIGNED</u>	<u>REVIEW</u>	<u>NUM</u>	<u>LET</u>	<u>ST</u>
ORIGINAL	AMENDMENT	22Dec95	26Dec95	16Jan96		1		
BC (Secifarma)	BZ (Stability)	27Jun96	02Jul96	10Jul96		1		
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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<sub>1</sub>  
treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

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tablet

STRENGTHS:

50 mg diclofenac sodium/ 200 µg misoprostol  
75 mg diclofenac sodium/ 200 µg misoprostol

ROUTE OF ADMINISTRATION:

oral

DISPENSED:

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.

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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)

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9/10/97

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

APPEARS THIS WAY  
ON ORIGINAL

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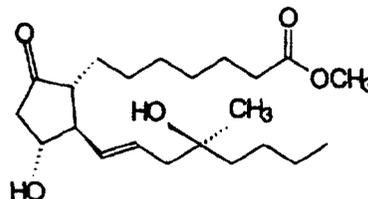
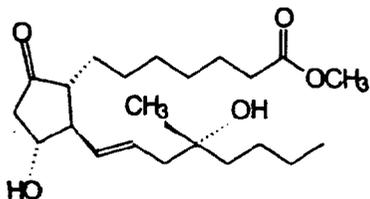
9/10/97

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





SUPPORTING DOCUMENTS:

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3. Division of Pharmaceutical Evaluation II, HFD-870 (Dr. Lydia Kaus)	15Feb96	<b>Pending</b> Dissolution Spec proposal to perform dissolution on enteric coated
4. Labeling and Nomenclature Committee, HFD-530 (Dr. Dan Boring)	02Feb96 06May96(Let)	<b>Acceptable</b> 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, and 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.

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

**/S/**

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

**/S/**

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

12/4/96

12/4/96

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

<u>SUBMISSION TYPE</u>	<u>DOCUMENT</u>	<u>CDER</u>	<u>DATES</u>		<u>NUM</u>	<u>LETTER</u>	<u>ST</u>
			<u>ASSIGNED</u>	<u>REVIEW</u>			
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<sub>1</sub>  
- 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:**  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

**APPEARS THIS WAY  
ON ORIGINAL**

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/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**





**REQUEST FOR TRADEMARK REVIEW**

*Handwritten signature and circled number 44*

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

<b>From:</b> Division of Gastrointestinal and Coagulation Drug Products	<b>HFD-180</b>
<b>Attention:</b> Brian Strongin	<b>Phone:</b> (301) 443-0483
<b>Date:</b> February 2, 1996	
<b>Subject:</b> Request for Assessment of a Trademark for a Proposed New Drug Product	
<b>Proposed Trademark:</b> Arthrotec	<b>NDA#</b> 20-607
<b>Established name, including dosage form:</b> diclofenac sodium/misoprostol tablets	
<b>Other trademarks by the same firm for companion products:</b> N/A	
<b>Indications for Use (may be a summary if proposed statement is lengthy):</b> 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.	
<b>Initial Comments from the submitter (concerns, observations, etc.):</b> No concerns at this time.	

**Note:** Meetings of the Committee are scheduled for the 4<sup>th</sup> 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**