CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-448

CHEMISTRY REVIEW(S)

only 2.1

SEP 27 1994

NDA 20-448

McNeil Consumer Products Company
Attention: Paula Oliver
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Oliver:

Please refer to your New Drug Application (NDA) submitted March 14, 1994 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium A-D (Loperamide) Chewable Tablets.

We also refer to your amendments dated April 21 and 26, and May 20, 1994.

We have completed the review of the chemistry portion of your submissions, and have the following recommendations and requests:

NDA 20-448

A freedom of information copy (FOIA) of the EA must be submitted. As a public document, the FOIA EA should be purged of confidential information, but be adequate to support a Finding of No Significant Impact (FONSI).

In order to continue their review, the Division of Biopharmaceutics is requesting the following information:

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

9/23/94
9/26/94

9/26/94

cc:
Orig NDA
HFD-180
HFD-180/GChen
HFD-180/CSO
R/D init: GChen 9/15/94
JGibbs, 9/16/94
SFredd 9/22/94
kj/September 7, 1994/c:\wpfiles\cso\n\20448409.0kj
IR

7-1 JUL 22 1997

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

NDA #: 20-448 CHEM.REVIEW #: 5 REVIEW DATE: May 28, 1997

SUBMISSION TYPE	DOCUMENT	CDER	ASSIGNED	DATES REVIEW	NUM	LETTER	ST
ORIGINAL	14Mar94	15Mar94	25Mar94	27Jul94	1	27Sep94	AE
AMENDMENTS							
BS	21Apr94	22Apr94					
BC	26Apr94	28Apr94	29Apr94	27Jul94	1	27Sep94	AE
BC	20May94	23May94	25May94	27Jul94	1	27Sep94	AE
ORIG. (EA)	14Mar94	15Mar94	25Mar94	27Jul94	2	27Sep94	AE
AC	13Dec94	14Ced94	20Dec94	08Feb95	3	15Mar95	AE
BC	27Jan95	30Jan95	03Feb95	08Feb95	3	15Mar95	AE
BC	22Sep95	25Sep95	06Nov95	20May96	4	14Jun96	AE
BC	21Dec95	22Dec95	27Dec95	20May96	4	14Jun96	AE
BC	11Mar96	12Mar96	13Mar96	20May96	4	14Jun96	AE

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Products
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME
Proprietary: IMODIUM A-D Chewable Tablets
Nonproprietary/USAN: loperamide HCl
Code Name/#:
Chem.Type/Ther.Class:

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

PHARMACOL.CATEGORY/INDICATION:

antidiarrheal

DOSAGE FORM: Chewable Tablet
STRENGTHS: 2 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: _____ Rx __X__ OTC

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

SUPPORTING DOCUMENTS:
See Chemistry Review #1

RELATED DOCUMENTS (if applicable):

Document	Date	Comments
Meeting Minutes	30Oct96	Adequate sampling plans requirements- size of sample, statistical criteria, and data analysis to support sampling plan- were discussed. Environmental assessment requirements were discussed. These meeting minutes conveyed to McNeil the requirements for addressing the deficiencies in their sampling plan.

CONSULTS:

Type	Division	Date	Status	Comments
Expiration Dating	Div.of Biostat.	04Feb97	Pending	18 mo Stability Data
Sampling	Div.of Biostat.	04Feb97	Pending	Sampling Plan

REMARKS/COMMENTS:
See Chemistry Review #1.

CONCLUSIONS & RECOMMENDATIONS:
Although the two consults to the Division of Biostatistics remain outstanding the NDA is recommended for APPROVAL.

cc:
Orig. NDA 20-448
HFD-180/Division File
HFD-180/GChen
HFD-180/BStrongin
R/D Init by: SUPERVISOR

filename: 20448703.5qc

7/22/97

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

7/22/97

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

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

NDA 20-448 CHEM.REVIEW: #4 REVIEW DATE: 20May96 JUN 17 1996

SUBMISSION TYPE

	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
ORIG. AMEND.	14Mar94	15Mar94	25Mar94	27Jul94	1	27Sep94	AE
BS	21Apr94	22Apr94					
BC	26Apr94	28Apr94	29Apr94	27Jul94	1	27Sep94	AE
BC	20May94	23May94	25May94	27Jul94	1	27Sep94	AE
ORIG. (EA)	14Mar94	15Mar94	25Mar94	27Jul94	2	27Sep94	AE
AC	13Dec94	14Dec94	20Dec94	08Feb95	3	15Mar95	AE
BC	27Jan95	30Jan95	03Feb95	08Feb95	3	15Mar95	AE

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Products Company
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME
Proprietary: IMODIUM® A-D Chewable Tablets
Nonproprietary/USAN: Loperamide HCl
Code Name/#:
Chem.Type/Ther.Class: 3S

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:
Antidiarrheal, Meperidine Congener (Opiod Receptor)
Controls the symptoms of diarrhea, including travelers' diarrhea

DOSAGE FORM: Chewable Tablet
STRENGTHS: 2 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _____ Rx __X__ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See USP 23

SUPPORTING DOCUMENTS:
See Chemistry Review #1.

BC Amendment 21Dec95

CONCLUSIONS & RECOMMENDATIONS:

The NDA remains approvable (AE). Deficiencies in sampling, manufacturing sites and environmental information should be conveyed to the firm.

6/14/96

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

6/17/96

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

cc:
Orig. NDA 20-448
HFD-180/Division File
HFD-180/BStrongin
HFD-180/GChen
R/D Init:EDuffy/6-12-96
GC/dob **F/T 6-12-96**/WP: c:\wpfiles\chem\N\20448602.4gc

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

NDA:20-448 CHEM REVIEW #2 REVIEW DATE: 8 FEB 1995 MAR - 9 1995

SUBMISSION TYPE	DATES						
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL	14Mar94	15Mar94	25Mar94	27Jul94	1	27Sep94	AE
BS	21Apr94	22Apr94					
BC	26Apr94	28Apr94	29Apr94	27Jul94	1		AE
BC	20May94	23May94	25May94	27Jul94	1		AE
AC	13Dec94	14Dec94	20Dec94	08Feb95	2		AE
BC	27Jan95	30Jan95	03Feb95	08Feb95	2		AE

NAME & ADDRESS OF APPLICANT :
McNeil Consumer Products Company
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME:
Proprietary: IMODIUM A-D Chewable Tablets
Nonproprietary/USAN: loperamide HCl
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY antidiarrheal

INDICATION: controls the symptoms of diarrhea, including Travelers' diarrhea

DOSAGE FORM: chewable tablet

STRENGTH: 2 mg

ROUTE OF ADMINISTRATION: oral

HOW DISPENSED: ___Rx _X_OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See USP 23 (1995)

SUPPORTING DOCUMENTS:
See Chemistry Review #1

RELATED DOCUMENTS (if applicable)

AUG 25 1994

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

NDA 20-448 **CHEM REVIEW #** 2 **REVIEW DATE:** August 1, 1994

SUBMISSION TYPE	DATES						
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL (EA)	14Mar94	15Mar94	19Apr94	01Aug94	2	2	NA

NAME & ADDRESS OF APPLICANT :
McNeil Consumer Products Company
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME:
Proprietary: IMODIUM^{R} A-D Chewable Tablets
Nonproprietary/USAN: Loperamide HCl
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY: Antidiarrheal

INDICATION: Controls the symptoms of diarrhea, including Travelers' Diarrhea

DOSAGE FORM: Chewable Tablet

STRENGTH: 2 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: ___ Rx __X__ OTC

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

SUPPORTING DOCUMENTS:
See Chemistry Review #1.

RELATED DOCUMENTS (if applicable):

CONSULTS: None

REMARKS/COMMENTS:
An approved environmental assessment and Finding of No Significant Impact (FONSI) has not been issued for any of the approved NDAs for loperamide Hcl.

CONCLUSIONS & RECOMMENDATIONS:
The environmental assessement is not approvable. No environmental assessment information has been provided for the drug substance site. The demonstration that the emissions to the environment from the manufacture of the drug substance and product will remain within permit limits is deficient (Item 6). No fate and effects testing is provided for the loperamide HCl. See Draft of Deficiency Letter for all of the deficiencies.

8/24/94

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

8/25/94

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20-448
HFD-180
HFD-180/SFredd
HFD-181/KJohnson
HFD-180/GChen
R/D Init by: JGibbs/8-22-94
GC/dob **F/T 8-23-94**\Wp: c:\wp51\chem\N\20448407.2GC

20448406.1GC

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

NDA:# 20-448 **CHEM REVIEW #** 1 **REVIEW DATE:** 27-Jul-94- AUG 12 1994

SUBMISSION TYPE	DATES						
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM	LETTER	ST
ORIGINAL	14Mar94	15Mar94	25Mar94	27July94	1		AE
AMENDMENTS							
BS	21Apr94	22Apr94					
BC	26Apr94	28Apr94	29Apr94	27July94	1		AE
BC	20May94	23May94	25May94	27July94	1		AE

NAME & ADDRESS OF APPLICANT :
McNeil Consumer Products Company
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME:
Proprietary: IMODIUM® A-D Chewable Tablets
Nonproprietary/USAN: Loperamide HCl
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY antidiarrheal

INDICATION: Controls the symptoms of diarrhea, including Travelers' Diarrhea

DOSAGE FORM: Chewable Tablet

STRENGTH: 2 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: __Rx __X_OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

SUPPORTING DOCUMENTS:
See Attachment from BC amendment of April 26, 1994.

RELATED DOCUMENTS (if applicable):

CONSULTS:

Division	Consult Date	Status	Comment
The Division of Biopharmaceutics	28Jun94	Pending	dissolution method and specifi-cation
The Division of Biometrics HFD-715	25May94	Pending	Expiration Dating

REMARKS/COMMENTS:

BC amendment of 26Apr94 contains a tabular list of all the supporting document and provides specific reference by submission date to the supporting information.

BC amendment of 20May94 contains the following:

-completed batch record for the biobatch C-130-9H
-dissolution methodology:
sample preparation by grinding the chewable tablet,
dissolution media at pH 4.7,
-dissolution data on whole tablet
-FD-483 for Round Rock, Texas.

CONCLUSIONS & RECOMMENDATIONS:
This application is "approvable" (AE) from consideration of chemistry manufacture and control pending an adequate response to the deficiency letter, and a satisfactory EIR.

8/12/94

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

8/12/94

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
NDA 20-448