CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020951

CHEMISTRY REVIEW(S)

Kaauba

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

NDA: 20-951 **CHEM REVIEW #4** **REVIEW DATE: June 7, 1999**
JUN 15 1999

SUBMISSION TYPE DATES

DOCUMENT	CDER	ASSIGNED
BL AMENDMENT	May 27, 99	June 4, 99

NAME & ADDRESS OF APPLICANT:
Smith Kline Beecham
1500 Littleton Road
Parsippany, NJ 07054-3884

DRUG PRODUCT NAME:

Proprietary:	TAGAMET HB 200™
Nonproprietary/USAN:	Cimetidine
Chem.Type/Ther.Class:	Type 3 New Formulation

PHARMACOLOGICAL CATEGORY: H_2 receptor histamine antagonist

INDICATION: Prevention and treatment of heartburn, acid indigestion and sour stomach

DOSAGE FORM: Suspension

STRENGTH: 200 mg/ml

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
[redacted]

CONSULTS: None

REMARKS/COMMENTS:
This amendment is a revised draft labeling to replace that previously provided to the Agency on Jan 8, 1999 for Nonprescription Tagamet HB 200™ Suspension. This submission comprises front and back labels for review (full color mockups) and demonstration folded back labels as they will appear in the pack.

CONCLUSIONS & RECOMMENDATIONS:
From the standpoint of chemistry, the information provided in the label is adequate.

/S/ [redacted] 6/15/99
Maria Elena Ysern, MSc.
Review Chemist, HFD-180

/S/ [redacted] 6/15/99
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

APPEARS THIS WAY ON ORIGINAL

cc:
NDA 20-951
HFD-180/LTalarico
HFD-180/Div File/NDA 20-951
HFD-180/EDuffy
HFD-180/MYsern
HFD-181/AKacuba
R/D Init by EDuffy/6-14-99
MY/dob **F/T 6-14-99/Word:** N:\wordfiles\chem\N\20951905.4MY

APPEARS THIS WAY ON ORIGINAL

Kacuba

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

JUN 10 1999

NDA: 20-951 **CHEM REVIEW #3** **REVIEW DATE: May 26,1999**

SUBMISSION TYPE DATES

	DOCUMENT	CDER	ASSIGNED
AMENDMENT	4/30/99	5/3/99	5/11/99

NAME & ADDRESS OF APPLICANT:
Smith Kline Beecham
1500 Littleton Road
Parsippany, NJ 07054-3884

DRUG PRODUCT NAME:

Proprietary:	TAGAMET HB 200™
Nonproprietary/USAN:	Cimetidine
Chem.Type/Ther.Class:	Type 3 New Formulation

PHARMACOLOGICAL CATEGORY: H_2 receptor histamine antagonist

INDICATION: Prevention and treatment of heartburn, acid indigestion and sour stomach

DOSAGE FORM: Suspension
STRENGTH: 200 mg/ml
ROUTE OF ADMINISTRATION: Oral
HOW DISPENSED: OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
[redacted]

CONSULTS: None

REMARKS/COMMENTS:
This amendment is a reply to an FDA letter of April 2, 1999 requesting additional Chemistry, Manufacturing and Controls information.

CONCLUSIONS & RECOMMENDATIONS: The information provided is adequate. The EER was resubmitted, plants were acceptable as of January 1998. The Methods Validations will be sent to the FDA laboratories for testing. From the stand point of chemistry NDA 20-951 may be approved. **Note: Labeling is pending. OTC has been requested to send a copy of the proposed labeling.**

/S/ [redacted] 6/8/99
Maria Elena Ysern, MSc.
Review Chemist, HFD-180

/S/ [redacted] 6/12/99
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-951
HFD-180/L.Talarico
HFD-180/Div File/NDA 20-951
HFD-180/E.Duffy
HFD-180/M.Ysern
HFD-181/CSO/A.Kacuba
R/D Init by EDuffy/6-1-99
MY/dob **F/T 6-8-99**/WORD: n:\wordfiles\chem\N\20951905.3MY

APPEARS THIS WAY ON ORIGINAL

CSO/Kamboa

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

NDA: 20-951 **CHEM REVIEW:** # 2 **REVIEW DATE:** Jan 8. 1998

SUBMISSION TYPE	**DATES**			
	DOCUMENT	**CDER**	**ASSIGNED**	**REVIEW**
AMENDMENT	11-20-98	11-23-98	2-3-98	Jan 8, 1998

NAME & ADDRESS OF APPLICANT:
Smith Kline Beecham
1500 Littleton Road
Parsippany, NJ 07054-3884

MAR 30 1999

DRUG PRODUCT NAME:

Proprietary:	TAGAMET HB 200™
Nonproprietary/USAN:	Cimetidine
Chem.Type/Ther.Class:	Type 3 New Formulation
PHARMACOLOGICAL CATEGORY:	H_2 receptor histamine antagonist
INDICATION:	Prevention and treatment of heartburn. acid indigestion. and sour stomach
DOSAGE FORM:	Suspension
STRENGTH:	200 mg/ml
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENSED:	OTC

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

[redacted]

CONSULTS:

[redacted]

REMARKS/COMMENTS:

This amendment is a response to the Agency's information request letter of November 6. 1998.

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

The information provided by the company adequately addresses the questions presented to the company by the FDA; but some additional information needs to be provided. Please refer to the deficiency letter.

/S/ [redacted] 3/29/99

Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ [redacted] 3/30/99

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

cc:

NDA 20-951
HFD-180/LTalarico
HFD-180/Div File/NDA 20-951
HFD-180/EDuffy
HFD-180/MYsern
HFD-181/CSO/AKacuba
R/D Init by:EDuffy/3-29-99
MY/dob F/T 3-29-99/WORD: n:\wordfiles\chem\N\20951812.2MY

APPEARS THIS WAY ON ORIGINAL

CSO/Kacuba

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-951 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 9\4\98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Dec 29, 1997	Dec 30, 1997	Jan 10, 1998
Amendment BC	Jun 6, 1998	Jun 17, 1998	Jun 19, 1998

NAME & ADDRESS OF APPLICANT:
Smith Kline Beecham
1500 Little Town Road
Parsimony, NJ 07054-3884

OCT - 8 1998

DRUG PRODUCT NAME

Proprietary: Tagamet HB 200®
Nonproprietary/USAN: Cimetidine
Code Name/#:
Chem.Type/Ther.Class: Type 3 New formulation

ANDA Suitability Petition/DESI/Patent Status:
Applicable patent numbers and expiration date of each:

Patent Number	Type of patent	Patent Owner	Expiration date
4,786,735	Process	SmithKline Beechman Cor	2008
4,996,222	Formulation	SmithKline& French Lab.	2011

PHARMACOL.CATEGORY/INDICATION:
H_2 receptor histamine antagonist.
Prevention and treatment of heartburn, acid indigestion and sour stomach.

DOSAGE FORM: Suspension
STRENGTHS: 200 mg/20 ml
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___ Rx ___X___ OTC

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

N''-Cyano-N-methyl-N'[2-[[5-methyl-1H-imidazol-4-yl)methyl]-thio]ethyl]guanidine.

Structure: See USP dictionary.
Molecular weight: 252.34
Molecular Formula: $C_{10}H_{16}N_6S$
Registry Name CAS: CAS-51481-61-9

SUPPORTING DOCUMENTS:

[redacted]

Also IND [redacted]

RELATED DOCUMENTS (if applicable):

CONSULTS:
Biopharm consult was sent to verify that the suspension formulation is bioequivalent to the approved tablet formulation.

REMARKS/COMMENTS:
This new non-prescription dosage form (suspension) of Tagamet HB 200® (Cimetidine) has been developed containing 200 mg of Cimetidine

per 20 ml as an alternative for consumers who have difficulty swallowing tablets or who prefer a liquid form. This dosage form has advantages in terms of palatability and stability.

Non-prescription Cimetidine suspension will be indicated for the same approved uses as non-prescription Cimetidine 200 mg tablets: prevention and relief of heartburn, acid indigestion and sour stomach. Cimetidine is a specific competitive histamine H_2-receptor antagonist that inhibits the secretion of histamine stimulated gastric acid.

Cimetidine has been manufactured to date as [redacted] and used in the manufacture of marketed solid oral dose (tablets) formulations because of its superior [redacted] characteristics. The specifications and control directions for Cimetidine [redacted] are provided in NDAs 17-920 and 20-398 for Tagamet® (prescription) and Tagamet HB® (OTC) tablets respectively.

[redacted]

APPEARS THIS WAY ON ORIGINAL

Cimetidine suspension formula marketed in the United Kingdom:

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

This application is approvable pending the resolution of the chemistry issues that will be listed in the deficiency letter.

cc:
Orig. NDA 20951803.1my
HFD-180/Division File
DISTRICT OFFICE
HFD-180/MYsern
HFD-180/MFolkendt/ /S/ [redacted]
R/D Init by:E.Duffy
filename: MY/ **F/T 10-8-98** Wordn:\wordfiles\chem\n\20951806

/S/ [redacted] 10-8-98

Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ [redacted] 10/8/98

Eric P. Duffy, PhD
Division of Gastrointestinal and Drug Coagulation Products.
ONDC II CDER

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020951

PHARMACOLOGY REVIEW(S)

Jolkendt

NDA 20,951

FEB 26 1998

Review # 1

Sponsor & Address: SmithKline Beecham Consumer Health Care
Parsippany, N.J.

Date of Submission: December 29, 1997

Date of HFD-180 Receipt: December 31, 1997

Date of Review: February 25, 1998

Product Name: Tagamet HB 200®

Generic Name: Cimetidine

Dosage Form: Suspension 200 mg/20 ml (1%)

Pharmacologic Category: Histamine H_2-receptor antagonist

Composition:

Ingredient Name	% w/w	mg/dose (20 ml)
Purified Water [redacted]	[redacted]	[redacted]
Cimetidine [redacted]		
Microcrystalline Cellulose/Carboxymethyl-cellulose Sodium [redacted]		
Saccharin Sodium [redacted]		
Propylene Glycol [redacted]		
Propylparaben [redacted]		
Butylparaben [redacted]		
Xanthan Gum, [redacted]		
FD&C Blue #1 [redacted]		
Sucrose [redacted]		
[redacted]		
TOTAL		

Indications: For prevention and treatment of heartburn, acid indigestion and sour stomach.

Related NDAs: NDA 17,920 (Tagamet tablets, SmithKline Beecham)
NDA 20,238 (Nonprescription Cimetidine tablets, SmithKline Beecham)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

SUMMARY AND EVALUATION:

This NDA provides for Tagamet HB 1% suspension (200 mg cimetidine/20 ml) as a nonprescription therapy for the prevention and treatment of food and beverage induced heartburn, acid indigestion, and sour stomach. Tagamet is a well established approved therapeutic entity. Tagamet tablet form has been approved for use in the treatment of active duodenal ulcer, benign gastric ulcer, erosive gastroesophageal reflux disease and pathological hypersecretory conditions and in the maintenance therapy for duodenal ulcer after healing of an active ulcer. A tablet formulation of the nonprescription Tagamet HB® 200 has been approved for the prevention and relief of heartburn, acid indigestion and sour stomach. Since the drug has already been found to be safe and is the subject of several approved NDAs (tablet, liquid and injection forms) with extensive clinical exposure, there is no need for additional preclinical studies. Approval of this NDA is recommended by Pharmacology.

/S/ [redacted] 2/26/98
Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA
HFD-180
HFD-181/CSO
/S/ HFD-180/Dr. Choudary
~~HFD-180/Dr. Talarico~~
[redacted]

JBC/hw/2/25/98
C:\WPFILES\PHARM\N\20951802.0JC

APPEARS THIS WAY ON ORIGINAL