

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020951**

**CHEMISTRY REVIEW(S)**

Kacuba

**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<sub>2</sub> 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:**

**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/

6/15/99

Maria Elena Ysern, MSc.  
Review Chemist, HFD-180

/S/

6/15/99

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

cc:

APPEARS THIS WAY ON ORIGINAL

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

Kauba

**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**

	<b>DOCUMENT</b>	<b>CDER</b>	<b>ASSIGNED</b>
<b>AMENDMENT</b>	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:	<b>TAGAMET HB 200™</b>
Nonproprietary/USAN:	Cimetidine
Chem.Type/Ther.Class:	Type 3 New Formulation

**PHARMACOLOGICAL CATEGORY:** H<sub>2</sub> 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:**


**CONSULTS:** None

**REMARKS/COMMENTS:**

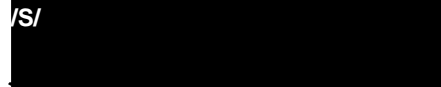
This amendment is a reply to an FDA letter of April 2, 1999 requesting additional Chemistry, Manufacturing and Controls information.

**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/

 6/21/99  
Maria Elena Ysem, MSc.  
Review Chemist, HFD-180

/S/

 6/21/99  
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.Ysem  
HFD-181/CSO/A.Kacuba  
R/D Init by EDuffy/6-1-99  
MY/dob F/T 6-8-99/WORD: n:\wordfiles\chem\N20951905.3MY

APPEARS THIS WAY ON ORIGINAL

CSO/Kambica

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

<b>NDA: 20-951</b>	<b>CHEM REVIEW: # 2</b>	<b>REVIEW DATE: Jan 8, 1998</b>		
<b>SUBMISSION TYPE</b>	<b>DATES</b>			
	<b>DOCUMENT</b>	<b>CDER</b>	<b>ASSIGNED</b>	<b>REVIEW</b>
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<sub>2</sub> receptor histamine antagonist

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

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

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



**CONSULTS:**

**REMARKS/COMMENTS:**  
This amendment is a response to the Agency's information request letter of November 6, 1998.

APPEARS THIS WAY ON ORIGINAL

**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  
[REDACTED]

CSD/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

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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<sub>2</sub> 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  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.

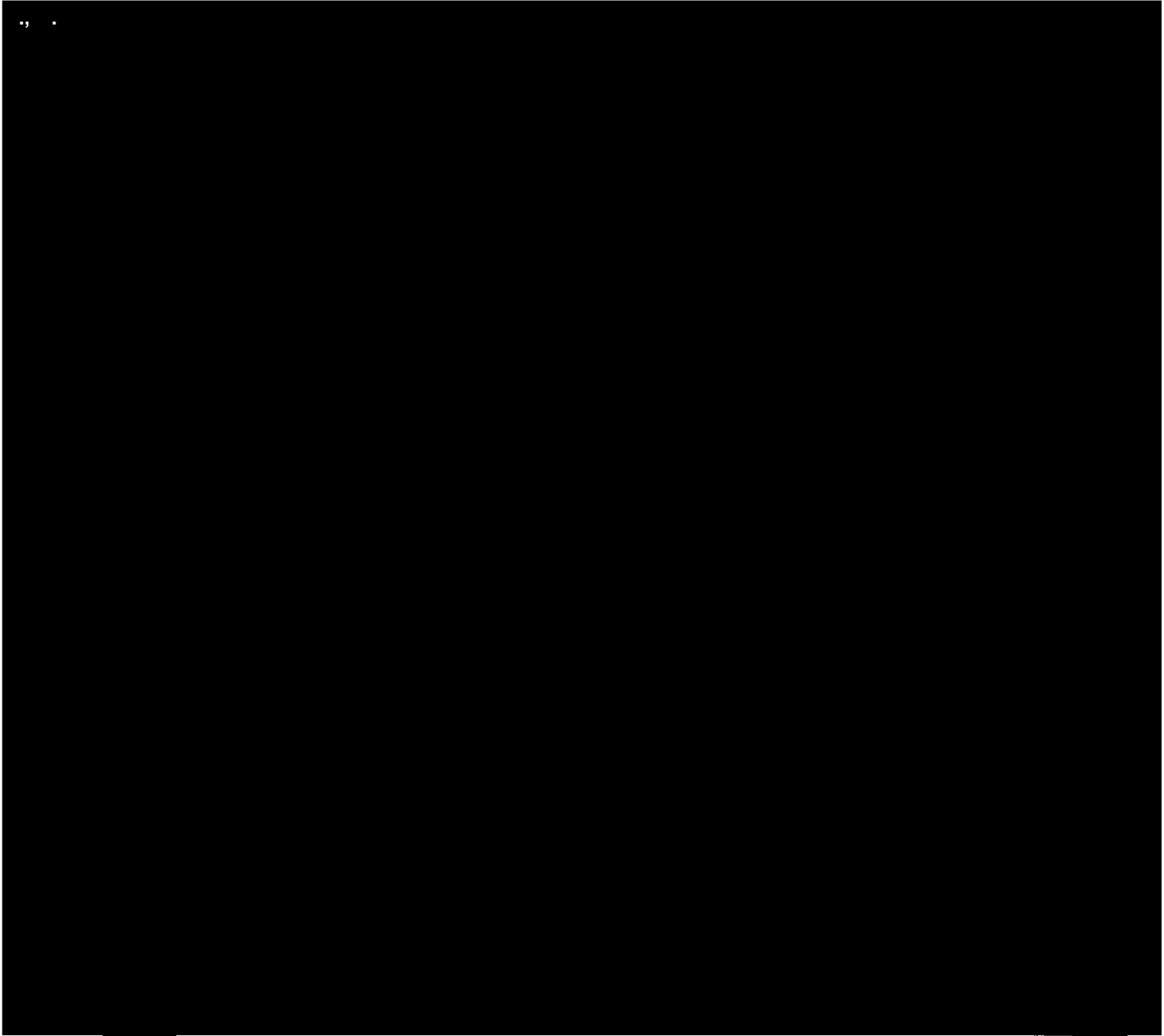
Molecular weight: 252.34

Molecular Formula: C<sub>10</sub>H<sub>16</sub>N<sub>6</sub>S

Registry Name CAS: CAS-51481-61-9



SUPPORTING DOCUMENTS:



Also IND

RELATED DOCUMENTS (if applicable):

CONSULTS:

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

REMARKS/COMMENTS:

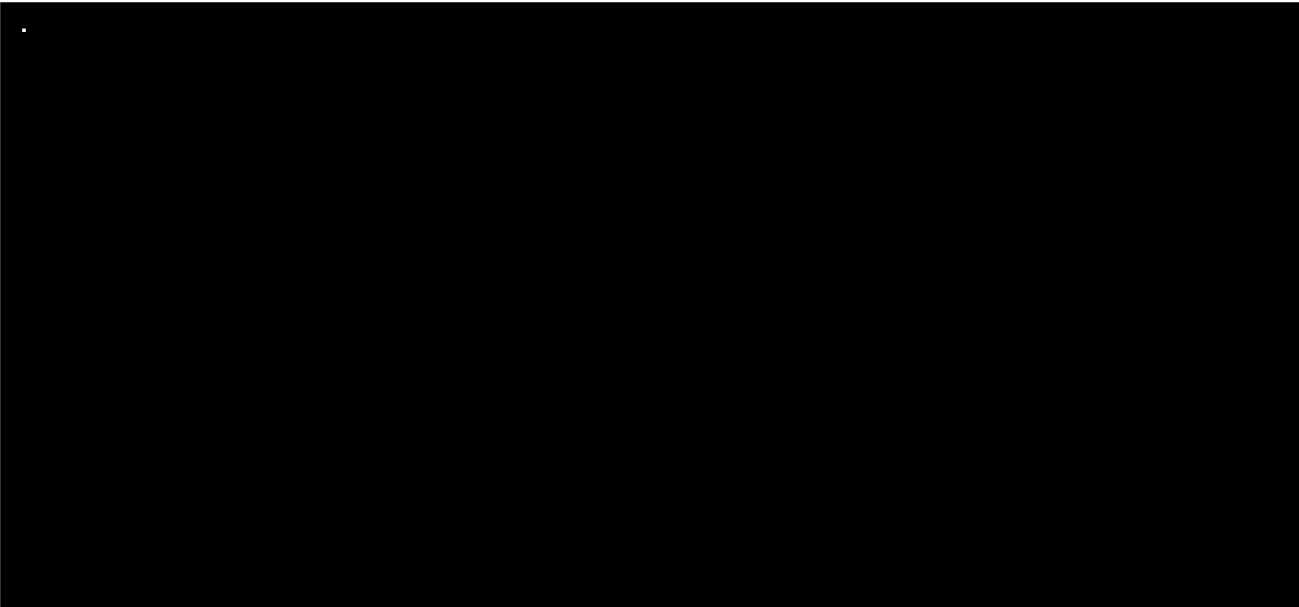
This new non-prescription dosage form (suspension) of Tagamet HB 200® (Cimetidine) has been developed containing 200 mg of Cimetidine

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.

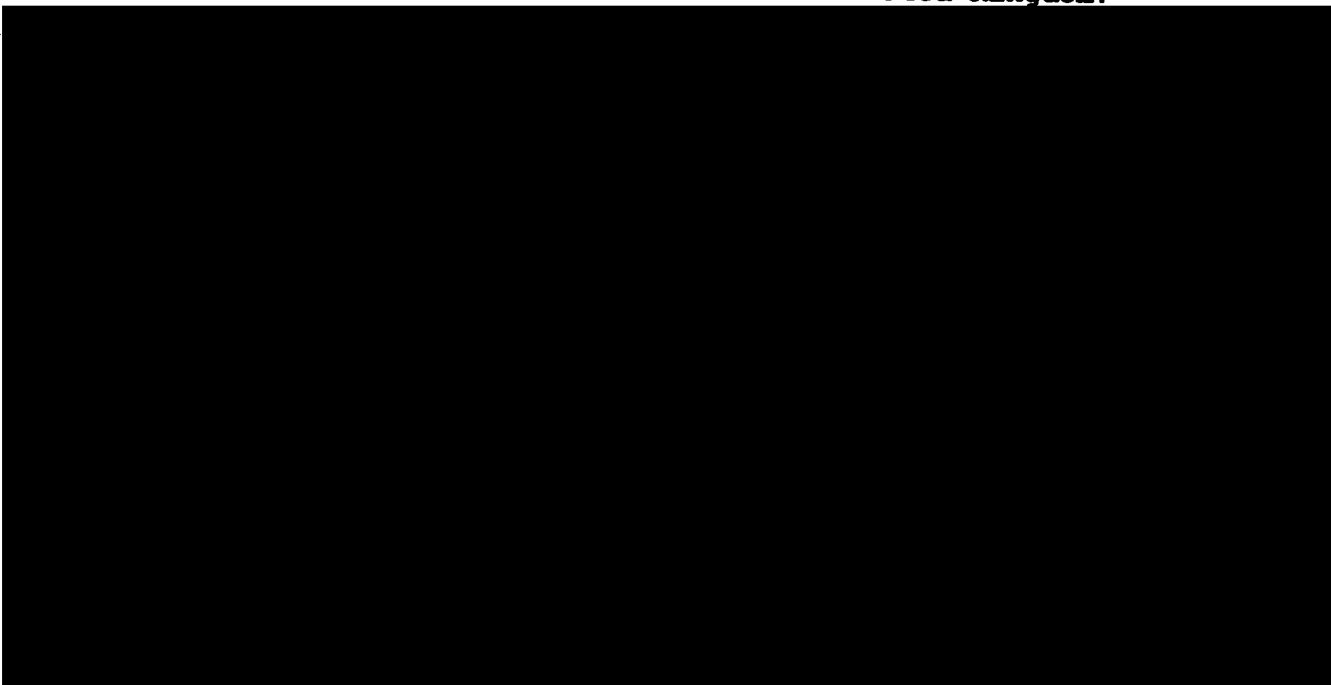
Cimetidine is a specific competitive histamine H<sub>2</sub>-receptor antagonist that inhibits the secretion of histamine stimulated gastric acid.

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.



APPEARS THIS WAY ON ORIGINAL

Cimetidine suspension formula marketed in the United Kingdom:



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]

cc/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)**

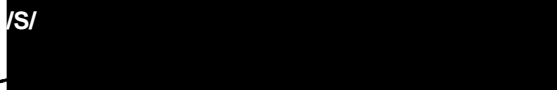


REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Original Summary

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/

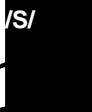
 2/26/98  
Jasti B. Choudary, B.V.Sc., Ph.D.

cc:

NDA

HFD-180

HFD-181/CSO

/S/  HFD-180/Dr. Choudary

~~HFD-180/Dr. Talarico~~

JBC/hw/2/25/98

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APPEARS THIS WAY ON ORIGINAL