

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020951

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

CSO/Kawla

NDA 20-951

DEC 17 1998

SmithKline Beecham Consumer Healthcare
Attention: Robert Harris
Senior Specialist, Regulatory Affairs
1500 Littleton Road
Parsippany, NY 07054-3884

Dear Mr. Harris:

Please refer to your new drug application (NDA) dated December 29, 1997, received December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nonprescription Tagamet HB 200[®] (cimetidine) Suspension.

We acknowledge receipt of your submissions dated February 13, June 16, and September 18, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following:

1. An adequate response to our letter dated November 6, 1998, requesting additional chemistry information. We acknowledge receipt of your submission dated November 20, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the issues cited in this letter.
2. Revised draft labeling, identical to that submitted September 18, 1998, modified as follows (requested revisions pertain to all bottle sizes unless otherwise specified):
 - a. Front of Bottle
 - i. Increase the legibility of the statement of identity (SOI), "Cimetidine Suspension 200 mg/Acid Reducer," by enlarging the type and printing it in a lighter color than that proposed (red).
 - ii. Include the following statement, prominently displayed: "Not for use by children under 12 years of age."

b. Outside of Opened Back Label

- i. Revise the statement of the dosage per unit to read: "Active Ingredient (in each 20mL): Cimetidine 200 mg."
- ii. Revise the second bullet statement in the "Uses" section to state, "For prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages." In addition, delete the bolding of the words "relief" and "prevention" in this section.
- iii. Revise the "Directions" section to state:

- For the second bullet statement, "To relieve symptoms, take 4 teaspoons or take 20 mL in premeasured dose cup provided, with a glass of water."
- For the third bullet statement, "To prevent symptoms, take 4 teaspoons or take 20 mL in premeasured dose cup provided, with a glass of water **right before or any time up to 30 minutes before** eating food or drinking beverages that cause heartburn."

If a dose cup is not provided in the **2 oz. Trial and 2 oz. Sample** size products, the above two bullet statements should delete any such reference.

- For the fourth bullet statement, "(4 teaspoons taken twice in 24 hours)" in place of "(up to 8 teaspoons in 24 hours)".
 - For the fifth bullet statement, "Children under 12 years of age: Not for use in children under 12 years of age. The safety and efficacy for OTC use in children under 12 years of age has not been proven."
- iv. Revise the tamper resistant/tamper evident statement to read, "Do not use if printed neck wrap is missing or torn." Follow the labeling requirements in the Final Rule Tamper-Evident Packaging Requirements for OTC Human Drug products.

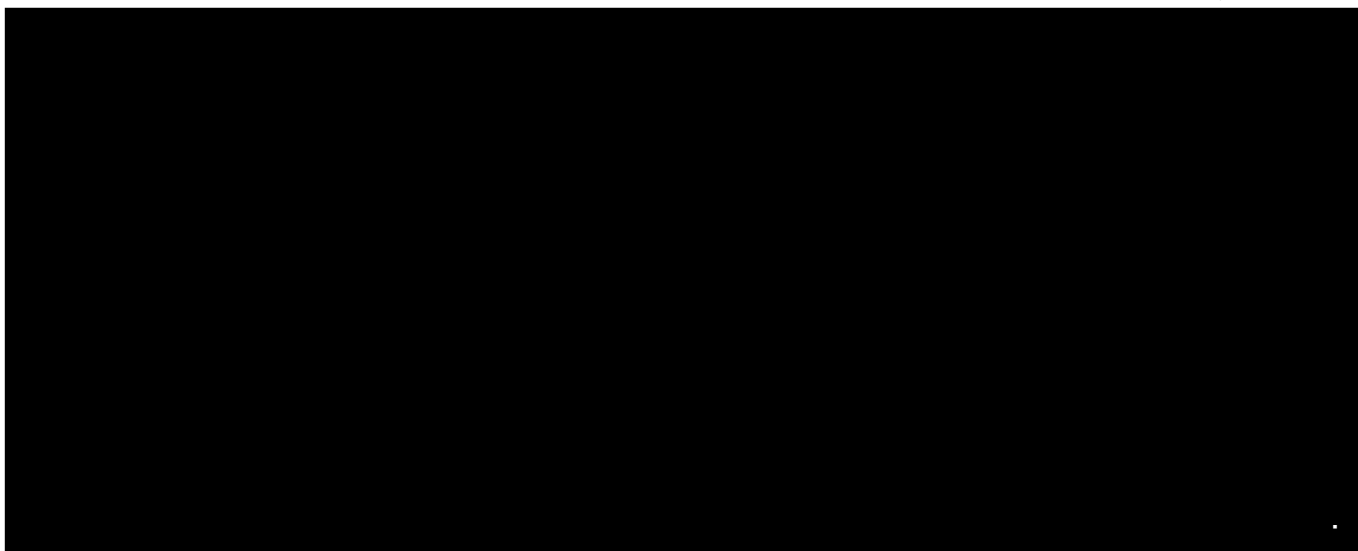
c. Inside of Opened Back Label

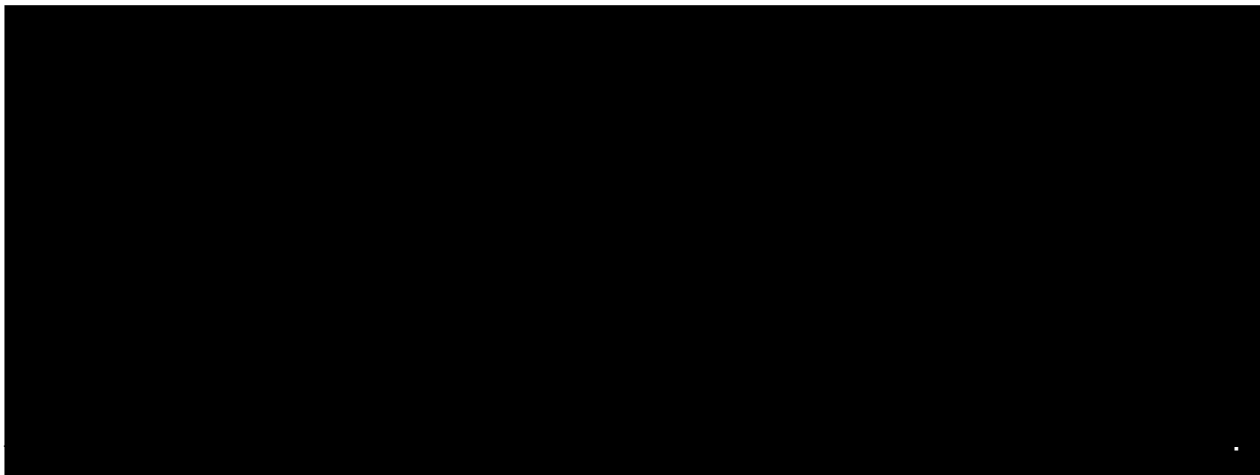
- i. Revise the storage statement to state, "Store between 20° - 30°C (68° - 86° F)".
- ii. Revise the first sentence under the header "Clinically Proven," to state the following: "In clinical studies, Tagamet HB 200 tablets were significantly better than placebo tablets (tablets without the medicine) in relieving and preventing heartburn symptoms. Tagamet HB 200 Suspension contains the same active ingredient."

- iii. Add the word "tablet" in the phrase "Tagamet HB 200" on the bar graphs.
- iv. For the 2 oz. Trial size container, add the header "Clinically Proven" to that portion of the labeling which contains the efficacy bar graphs comparing the efficacy of Tagamet HB to placebo.
- v. Revise the 2 oz Sample size container labeling to include the response rate graphs, revised as requested above.
- d. For all package presentations, clarify where the expiration date and lot number will be located.
- e. Verify that the statement "New Liquid" will be removed six months after initial marketing.
- f. Although not a requirement at this time, some of the information included under the heading "Drug Interaction Warning," should be incorporated into the warning section under the subheading "Ask a doctor before use...." or under the heading "Other Information", to be consistent with the format in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. Also, you may wish to consider including a section titled "Tips for Managing Heartburn" in your labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b), provide updated safety information you have regarding your new drug.





Finally, please submit four copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Gastrointestinal and Coagulation Drug Products, one to the Division of Over-the-Counter Drug Products, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

APPEARS THIS WAY ON ORIGINAL

If you have any questions regarding this application, please contact Alice Kacuba, Consumer Safety Officer, at (301) 827-7310.

Sincerely yours,

 /S/

12-17-98

Debra Bowen, M.D.
Acting Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

 /S/

12-17-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

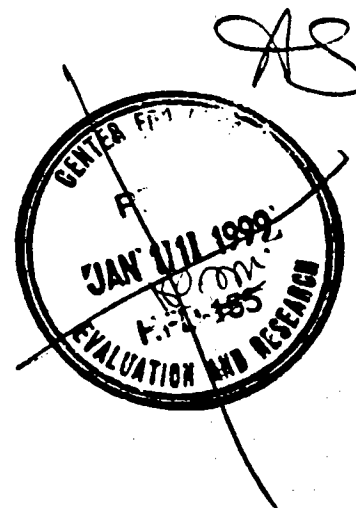
Doc Copy

SB
SmithKline Beecham
Consumer Healthcare

January 8, 1999

NDA 20-951
Non-Prescription Cimetidine Suspension 1%

Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-180)
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857



Re: Non-Prescription Tagamet HB 200[®] (cimetidine) Suspension
Response to FDA Approvable Letter of December 17, 1998

Dear Dr. Talarico,

Please refer to our approvable New Drug Application 20-951 for Tagamet HB 200[®] (cimetidine) Suspension and to the Agency's letter of December 17, 1998 requesting additional information for the approval of the application.

We are now replying (R) to those comments (*italicized*) in the same order as the Agency posed them.

1. *An adequate response to our letter dated November 6, 1998, requesting additional chemistry information. We acknowledge receipt of your submission dated November 20, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the issues cited in this letter.*
- R. Our submission of November 20, 1998 addresses all of the chemistry issues in the Agency's letter of November 6, 1998. Please reference that submission in its entirety as a complete response to the Agency's inquiries for additional chemistry information.
2. *Revised draft labeling, identical to that submitted September 18, 1998, modified as follows (requested revisions pertain to all bottle sizes unless otherwise specified).*
- R. We have enclosed revised draft labeling identical to that submitted on September 18, 1998 including all requested revisions with one exception. Item 2(a)(ii) has not been incorporated at this time.

We request that this issue be discussed as a general policy outside this NDA review so as not to further delay approval of this application. Please see the response for this item [2(a)(ii)] for a detailed explanation.

a. Front of Bottle

- i. Increase the legibility of the statement of identity (SOI), "Cimetidine Suspension 200mg/Acid Reducer," by enlarging the type and printing it in a lighter color than that proposed (red)*

R. The type size of the statement of identity (SOI), "Cimetidine Suspension 200mg/Acid Reducer," has been increased and the color of the print was changed from "red" to "yellow" to enhance the legibility of this statement. Due to the size of the front label for the 2-ounce (trial and sample) and 12-ounce containers, the request to increase the print size of the SOI did not allow the complete statement to remain on single line as originally submitted to the Agency.

The original decision to use the red color print for the SOI was to ensure consistency and harmonization with all previously approved labeling for Tagamet HB 200[®] tablets. However, as requested and mentioned above, the print color for the SOI has been changed from "red" to "yellow."

- ii. Include the following statement, prominently displayed: "Not for use by children under 12 years of age."*

R. SmithKline Beecham Consumer Healthcare is committed to OTC drug product labeling that provides appropriate consumer information to ensure safe and effective use of our products. As such, we are fully supportive of agency initiatives to address usage and labeling issues concerning the pediatric population (see Phase 4 commitment, page 8, item C).

We agree with the Agency's request [see item 2(b)(iii)] that the Directions for the use of Tagamet Suspension be revised to advise consumers that this product is not for use in children under 12 years of age.

However, at this time, we question the proposed requirement to include this Direction on the Principal Display Panel (PDP). To the best of our knowledge, this proposal is without precedent and outside current labeling provisions and requirements (21 CFR §201). We contend that the Directions statement suggested by the Agency for inclusion on the back label actually provides more appropriate, fully adequate directions for use, in a placement consistent both with consumer expectation and competitive market place practice.

We respectfully suggest that the Agency consider this labeling proposal outside this NDA review, as a broader policy issue. This approach, with associated procedural guidance and public comment, would provide an opportunity for discussion of label changes best serving public health and ensure a transparent evaluation process with fairness and consistency of implementation across OTC drug products.

b. Outside of Opened Back Label

i. Revise the statement of the dosage per unit to read: "Active Ingredient (in each 20mL): Cimetidine 200 mg."

R. The statement of the dosage per unit has been revised for the 2-ounce and 12-ounce container labels to read "Active Ingredient (in each 20 mL): Cimetidine 200 mg" as requested.

ii. Revise the second bullet statement in the "Uses" section to state, "For prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages." In addition, delete the bolding of the words "relief" and "prevention" in this section.

R. The second bullet statement in the "Uses" section has been revised to read "For prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages." Additionally, the words "relief" and "prevention" have been changed to standard print as requested by the Agency.

iii. Revise the "Directions" section to state:

• For the second bullet statement, "To relieve symptoms, take 4 teaspoons or take 20mL in premeasured dose cup provided, with a glass of water."

R. The second bullet statement of the "Directions" section for the 12-ounce container label has been revised to read "To relieve symptoms, take 4 teaspoons or take 20mL in premeasured dose cup provided, with a glass of water."

The second bullet statement of the "Directions" section for the 2-ounce trial and sample container labels has been revised to read "To relieve symptoms, take 4 teaspoons (20mL) with a glass of water." A dose cup is not provided with the 2-ounce trial and sample size containers.

Please note that we have included the statement "(20mL)" after 4 teaspoons in the "Directions" section of the labeling. The inclusion of this statement has been added to minimize any consumer confusion with the revised statement of dosage per unit requested by the Agency.

- *For the third bullet statement, "To prevent symptoms, take 4 teaspoons or take 20mL in premeasured dose cup provided, with a glass of water right before or any time up to 30 minutes before eating food or drinking beverages that cause heartburn."*

If a dose cup is not provided in the 2 oz. Trial and 2 oz. Sample size products, the above two bullets statements should delete any such reference.

- R. The third bullet statement of the "Directions" section for the 12-ounce container label has been revised to read "To prevent symptoms, take 4 teaspoons or take 20mL in premeasured dose cup provided, with a glass of water right before or any time up to 30 minutes before eating food or drinking beverages that cause heartburn."

The third bullet statement of the "Directions" section for the 2-ounce trial and sample container labels has been revised to read "To prevent symptoms, take 4 teaspoons (20mL) with a glass of water right before or any time up to 30 minutes before eating food or drinking beverages that cause heartburn."

Please note that we have included the statement "(20mL)" after 4 teaspoons in the "Directions" section of the labeling. The inclusion of this statement has been added to minimize any consumer confusion with the revised statement of dosage per unit requested by the Agency.

- *For the forth bullet statement, "(4 teaspoons taken twice in 24 hours)" in place of "(up to 8 teaspoons in 24 hours)."*
- R. The forth bullet statement of the "Directions" section for the 2-ounce (trial and sample) and 12-ounce container labels has been revised to read "Tagamet HB 200 can be used up to twice daily (4 teaspoons taken twice in 24 hours)."
- *For the fifth bullet statement, "Children under 12 years of age: Not for use in children under 12 years of age. The safety and efficacy for OTC use in children under 12 years of age has not been proven."*

- R. The fifth bullet statement of the "Directions" section for the 2-ounce (trial and sample) and 12-ounce container labels has been revised to read "Children under 12 years of age: Not for use in children under 12 years of age. The safety and efficacy for OTC use in children under 12 years of age has not been proven."
- iv. *Revise the tamper resistant/tamper evident statement to read, "Do not use if printed neck wrap is missing or torn." Follow the labeling requirements in the Final rule Tamper-Evident Packaging Requirements for OTC Human Drug products.*
- R. The tamper resistant/tamper evident statement for the 2-ounce (trial and sample) and 12-ounce container labels has been revised to read "Do not use if printed neck wrap is missing or torn."
- c. *Inside of Opened Back Label*
- i. *Revise the storage statement to state, "Store between 20° - 30°C (68° - 86° F)."*
- R. The storage statement for the 2-ounce (trial and sample) and 12-ounce container labels has been revised to read "Store between 20° - 30°C (68° - 86° F)."
- ii. *Revise the first sentence under the header "Clinically Proven," to state the following: "In clinical studies, Tagamet HB 200 tablets were significantly better than placebo tablets (tablets without the medicine) in relieving and preventing heartburn symptoms. Tagamet HB 200 Suspension contains the same active ingredient."*
- R. The first sentence under the header "Clinically Proven" for the 2-ounce (trial and sample) and 12-ounce container labels has been revised to read "In clinical studies, Tagamet HB 200 tablets were significantly better than placebo tablets (tablets without the medicine) in relieving and preventing heartburn symptoms. Tagamet HB 200 Suspension contains the same active ingredient."
- iii. *Add the word "tablet" in the phrase "Tagamet HB 200" on the bar graphs.*
- R. The word "tablet" has been added after each Tagamet HB 200 statement on the efficacy bar graphs contained on the 2-ounce (trial and sample) and 12-ounce container labels.

- iv. *For the 2oz. Trial size container, add the header "Clinically Proven" to that portion of the labeling which contains the efficacy bar graphs comparing the efficacy of Tagamet HB to placebo.*
- R. As requested by the Agency, the heading "Clinically Proven" was added to the section of the 2-ounce trial container label that contains the efficacy bar graphs.
- v. *Revise the 2 oz. Sample size container labeling to include the response rate graphs, revised as requested above.*
- R. The response rate graphs were added the 2-ounce sample size container label as well as all changes requested above for the efficacy bar graphs.
- d. *For all package presentations, clarify where the expiration date and lot number will be located.*
- R. The lot number and expiration date will be located on the outer edge of the back label for the 2-ounce (trial and sample) and 12-ounce size containers. This information will be clearly visible to the consumer at the point of purchase.
- e. *Verify that the statement "New Liquid" will be removed six months after initial marketing.*
- R. The word "New" will be removed from the front label six months after initial marketing. We are requesting that the word "Liquid" be retained on the front label to maintain consistent use of this word throughout the labeling as well as in the OTC market place. Please note that the word "New" will be only used on the front label of the 12-ounce size container.
- f. *Although not a requirement at this time, some of the information included under the heading "Drug Interaction Warning," should be incorporated into the warning section under the subheading "Ask a doctor before use..." or under the heading "Other Information", to be consistent with the format in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. Also, you may wish to consider including a section titled "Tips for Managing Heartburn" in your labeling.*
- R. We are considering incorporating all applicable information included under the heading "Drug Interaction Warning" into one of the sections suggested by the Agency to be consistent with the proposed labeling format for OTC drug products.

A section titled "Tips for Managing Heartburn" has been added to the 12-ounce container label. Due to space limitations for the 2-ounce trial and sample container labels, this section was not included on the labeling.

In accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b), provide updated safety information you have regarding your new drug.

- R. There is no additional safety data available beyond that previously submitted in the original application for Tagamet HB 200[®] Suspension. The application contained a single clinical study comparing the relative bioavailability of cimetidine oral suspension (200mg/20mL) versus cimetidine 200mg tablets.

In our February 13, 1998 submission for Tagamet HB 200[®] Suspension, we provided tabulated data listings of all Adverse Experiences (AEs) reported through February 13, 1998 for the Cimetidine Suspension products [REDACTED]

[REDACTED] There are no additional AEs reported for these products through December 31, 1998. Please note that Tagamet Dual Action Liquid was discontinued in the UK in January 1998 for marketing reasons, not for safety reasons.





Finally, please submit four copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

- R. We will submit, when available, four draft copies of the introductory promotional materials that are planned to be used for Tagamet HB 200[®] Suspension. A copy of these promotional materials will be submitted to the Division of GI and Coagulation Drug Products, and Division of OTC Drug Products, and two copies of both the promotional materials and the package insert will be forwarded directly to the Division of Drug Marketing, Advertising, and Communications for evaluation.

We trust this response is satisfactory and will enable the Agency to approve our application. If you have any questions or comments concerning this matter, please contact me at (973) 889-2513 or Sue James at (973) 889-2561.

Sincerely,

Robert Harris
Senior Regulatory Affairs Specialist
SmithKline Beecham Consumer Healthcare
I:BobH/Tagamet/Tagamet Susp/Response to FDA approvable Letter.doc

- Encl. FDA Form 356h
Revised draft labeling for 12-ounce size container
Revised draft labeling for 2-ounce trial and sample size containers
Draft Shrink band labeling for 2-ounce and 12-ounce size containers

JUN 30 1999

MEMORANDUM

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

DATE: June 30, 1999
FROM: Director,
Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review
Tagamet HB Suspension
NDA 20-951

TO: Director,
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

Attached is OTC's review of the draft labeling submitted by SmithKline Beecham for the subject NDA.

 /S/

Charles J. Ganley, M.D.

JUN 30 1999

**Division of Over-the-Counter Drug Products
Labeling Review**

NDA: 20-951
SUBMISSION TYPE: New Drug Application - Drug Facts Labeling
SPONSOR: SmithKline Beecham
DRUG PRODUCT: Tagamet HB 200 Suspension
INDICATIONS: Relieves heartburn, acid indigestion, and sour stomach
Prevents these symptoms brought on by consuming food and beverages
ACTIVE INGREDIENT: Cimetidine 200 mg per 20mL
SUBMISSION DATES: January 8, and May 27, 1999
REVIEWER: Albert Rothschild
REVIEW DATE: June 22, 1999
PROJECT MANAGER: Albert Rothschild

A. BACKGROUND:

In a letter of January 8, 1999, the sponsor responded to the Agency's approvable letter of December 17, 1998, for Tagamet HB Suspension and made all requested changes, except that the statement "Not for use in children under 12 years of age" was not added to the PDP as requested but is present in the "Directions" section. (See attachment 1.) Also, the labeling was not in compliance with the OTC Labeling Requirements Final Rule (64 FR 13254) published March 17, 1999. Subsequently, on May 27, 1999, the sponsor submitted revised labeling, in Drug Facts format, for the 12 oz. retail bottle, 2 oz trial size bottle, and 2 oz sample size bottle. The sponsor notes that "the small package labeling provisions as described in the Final Rule were applied to both the 2 oz. retail and 2 oz. sample size bottles." In addition to the specific information required by § 201.66, the label includes information on interactive drug trade names, graphs showing drug vs. placebo effectiveness, a description of heartburn, and tips for managing heartburn. (See attachment 2.) In a letter of June 17, 1999, the sponsor submitted representative sample 2 oz. trial and sample size bottles, and the 12 oz. retail bottle with the respective labels attached.

APPEARS THIS WAY ON ORIGINAL

B. THE 2 FLUID OZ. TRIAL AND 2 FLUID OZ. SAMPLE SIZE BOTTLE LABELS.

The sponsor's application of "the small package labeling provisions as described in the Final Rule" to both the 2 oz. trial and 2 oz. sample size bottles is inappropriate. The final rule, in § 201.66(d)(10), provides that if the Drug Facts required information and any other FDA required information for drug products, requires more than 60% of the label surface area, then exceptions to specific, listed Drug Fact requirements are permitted. (See attachment 3.)

The information required on the Tagamet Suspension label does not constitute 60% of the label. The information concerning interactive drug trade names, graphs showing drug vs. placebo effectiveness, a description of heartburn, and tips for managing heartburn is useful information for the consumer but should be placed in an accompanying package insert. Accordingly, such information is not counted toward the 60% "required information" and the label must meet all the requirements of § 201.66.

We will be able to comment further on the adequacy of the 2 fluid oz. bottle labels when the labels are resubmitted with all required information.

C. ALL BOTTLE LABELS.

The following comments are applicable to the 2 fluid oz. trial and sample size bottle labels and the 12 fluid oz. bottle label:

1. Visible Panel of the Folded Back Label:

So that there is no difficulty for the consumer to easily determine how to find the Drug Facts information, the direction "OPEN HERE" or "OPEN HERE FOR DRUG FACTS INFORMATION" on the visible panel of the folded back label, needs to be made more conspicuous and prominent.

2. Uses:

The sponsor should be requested to modify the words "for relief of" and "for prevention of" with "relieves" and "prevents," respectively, in the *Uses* section.

3. Warnings:

For consistency with § 201.66:

- a. Capitalize the first letter of the **Allergy alert** warning to read:
"Allergy alert: Do not use if you are allergic to cimetidine or other acid reducers."

- b. In the sponsor's letter of January 8, 1999, the sponsor did not agree to include the warning [REDACTED] on the PDP. Because of the Agency's concern that the suspension product may be used in children under 12 years of age without adequate evidence for safety and efficacy in this population, the sponsor again is requested to place the "Not for use in children under 12 years in the PDP or to place the statement in the **Warnings** section of the Drug Facts portion of the label. The statement should be placed as the first bulleted, bolded statement under the [REDACTED] section, as follows:
"• in children under 12 years (see Directions)"
- c. Under the subheading "Ask a doctor or pharmacist before use if you are," use upper and lower case letters for "THEOPHYLLINE," "THEO-DUR," "WARFARIN," and "PHENYTOIN." Because the choice of proprietary products is added at the sponsor's discretion, the prototype label attached does not identify the trade named products. The Agency has additional concerns that consumers not taking one of the specifically named products, may not recognize other similar products and continue to use them inappropriately.
- d. Left align the "Keep out of reach of children" warning.
4. **Directions:**
For consistency with other OTC drug product labels:
- a. In the second and third bullets, change the word [REDACTED] to read:
[REDACTED]
- b. Change the fourth bullet to read:
[REDACTED]
- c. To save label space and to promote safe use of the product by emphasizing (bolding) that the consumer should not use the product for children, change the fifth bullet to read:
[REDACTED]
- For consistency with § 201.66:
- d. Change the format so that the bulleted statements are aligned as reflected in the enclosed "ATTACHMENT 4 Proposed Draft H2 (Cimetidine Suspension) Drug Class Consumer Labeling."

NDA 20-951
DOTCDP Labeling Review,
June 22, 1999

5. **Other information**

For consistency with other OTC drug product labels, change the word [REDACTED] and remove the degree symbol from numbers [REDACTED] to read:

"• store at 20 - 30°C (68 - 86°F)"

6. **Questions or comments?**

For consistency with § 201.66:

Remove upper case letters from the phrase "Call Toll-Free" to read:
"call toll-free"

D. SUMMARY:

Actions that must be taken for further consideration of the application:

2 FLUID OZ. TRIAL AND 2 FLUID OZ. SAMPLE BOTTLE LABELS.

The label must be revised to meet all the requirements of § 201.66 for the standard labeling format (See item B above).

ALL BOTTLE LABELS.

The following changes must be made to the 2 fluid oz. trial and sample bottle labels and the 12 fluid oz. retail bottle label:

1. **Visible Panel of the Folded Back Label:**

So that there is no difficulty for the consumer to easily determine how to find the Drug Facts information, the direction "OPEN HERE" or "OPEN HERE FOR DRUG FACTS INFORMATION" on the visible panel of the folded back label, must be made more conspicuous and prominent.

2. **Warnings:**

For consistency with § 201.66:

a. Capitalize the first letter of the Allergy alert warning to read:
"Allergy alert: Do not use if you are allergic to cimetidine or other acid reducers."

b. The Agency prefers to place the [REDACTED] warning on the PDP. However, as a second preference to facilitate safe use of the product, the Agency would allow the sponsor to place the following bulleted, bolded statement under the "Warnings" ,
"Do not use" section:
"• in children under 12 years (see Directions)"

The sponsor should be advised that the warning must appear either on the PDP or in the **Warnings** section, in addition to the **Directions** section.

- c. Under the subheading "Ask a doctor or pharmacist before use if you are," use upper and lower case letters for "THEOPHYLLINE," "THEO-DUR," "WARFARIN," and "PHENYTOIN." Because the choice of proprietary products is added at the sponsor's discretion, the prototype label attached does not identify the trade named products. The Agency has additional concerns that consumers not taking one of the specifically named products, may not recognize other similar products and continue to use them inappropriately.
- d. Left align the "Keep out of reach of children" warning.

3. **Directions:**

For consistency with other OTC drug product labels:

- a. In the second and third bullets, change the word [REDACTED] to read:
[REDACTED]

- b. Change the fourth bullet to read:
[REDACTED]

- c. To save label space and to promote safe use of the product by emphasizing (bolding) that the consumer should not use the product for children, change the fifth bullet to read:
[REDACTED]

- d. For consistency with § 201.66:

Change the format so that the bulleted statements are aligned as reflected in the enclosed "ATTACHMENT 4 Proposed Draft H2 (Cimetidine Suspension) Drug Class Consumer Labeling."

4. **Other information**

For consistency with other OTC drug product labels, change the word
[REDACTED]

NDA 20-951
DOTCDP Labeling Review,
June 22, 1999

5. Questions or comments?

For consistency with § 201.66:

Remove upper case letters from the phrase "Call Toll-Free" to read:
"call toll-free"

In addition to the above, the sponsor should be requested to modify the words

[REDACTED]
in the *Uses* section.

We note that the sponsor has refused to add the children under 12 statement to the PDP. We are not aware of a provision in the law that would permit us to require that the statement be placed on the PDP.

RECOMMENDATION:

The application should not be approved until the changes cited above have been made and found acceptable.

[REDACTED] /S/

Albert Rothschild, B.S.
OTC Policy Analyst

[REDACTED] /S/

Heien Cothran, B.S.
Team Leader, HFD-560

[REDACTED] /S/

Linda M. Katz, M.D., M.P.H.
Deputy Director, HFD-560

ate signed 6/30/99

[REDACTED] APPEARS THIS WAY ON ORIGINAL

Attachments

7 Pages REDACTED
DRAFT LABELING

Falkend+

MEMORANDUM

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

DATE: 10/28/98

FROM: Acting Director
Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review
Tagamet HB 200 Suspension
NDA 20-951

TO: Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)

Attached is OTC's review of the draft labeling submitted by SmithKline Beecham Consumer Healthcare for the subject NDA.


Debra Bowen, M.D. *ISI*

APPEARS THIS WAY ON ORIGINAL

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**Division of Over-the-Counter Drug Products
Labeling Review**

NDA #: 20-951

SUBMISSION DATE: September 18, 1998

SUBMISSION TYPE: New drug application -- revised draft labeling

SPONSOR: SmithKline Beecham Consumer Healthcare

DRUG PRODUCT: Tagamet HB 200® Suspension

INDICATIONS: Relieves heartburn, acid indigestion and sour stomach
Prevents heartburn, acid indigestion and sour stomach brought on
by consuming food and beverages.

ACTIVE INGREDIENT: Cimetidine 200 mg per 20 mL

REVIEWER: Mary S. Robinson, M.S.

REVIEW DATE: October 16, 1998

PM: Al Rothschild

Background:

Tagamet HB 200® (cimetidine) tablets, 200 mg was approved for nonprescription use for the treatment of episodic heartburn, acid indigestion, and sour stomach on June 19, 1995 and the prevention of meal induced heartburn when taken 30 minutes before eating on August 21, 1996. On June 5, 1998, NDA 20-238/S-006 was approved for the prevention of heartburn symptoms when taken any time up to 30 minutes before eating. This submission (NDA 20-951), submitted on December 29, 1997, is for a new liquid (suspension) dosage form of the approved Tagamet HB® and Tagamet HB 200® drug products. Because of the recommended labeling changes made as a result of the June 5, 1998 approval of NDA 20-238/S-006, the sponsor resubmitted revised proposed labeling for Tagamet HB 200 suspension (NDA 20-951) that purportedly reflects the labeling changes approved for Tagamet HB 200® tablets (NDA 20-238/S-006). This review is based on full color mock-ups of draft labeling of the 12 fluid ounce bottle, 2 fluid ounce bottle, and 2 fluid ounce sample bottle for Tagamet HB 200® suspension. (See Attachments 1-13.)

I. Reviewer's Comments and Recommendations to Be Conveyed to the Sponsor:

NOTE: This drug product's back label has a "peel back" feature. (Please refer to the attached proposed labeling.) (See Attachments 1-13.)

A. Bottle, Liquid 12 FL. OZ 1. Front (Attachment 1).

- a. The statement of identity (SOI) "Cimetidine Suspension 200 mg /Acid Reducer" is correct and in conformity with 21 CFR 201.61. However, the SOI must be prominently displayed and readable. We recommend use of a lighter color to improve the readability of the SOI. We also recommend that the SOI be ½ the size of the proprietary name in all areas of the labeling, although this is not a regulatory requirement.
- b. The word "New Liquid" has been added to the labeling. This statement should

be removed after the first six months of OTC marketing.

- c. The front panel should include the statement "Not for use by children under 12 years of age."

2. Outside of Opened Back Label (Attachment 3).

- a. Active Ingredient.

[REDACTED]

DRAFT LABELING

This change should be made in all of the labeling. (See prototype label, Attachment 14.)

- b. Uses, bullet 2. The prevention indication stated in the June 5, 1998 approval letter for NDA 20-238/S-006 contained a typographical error. The "Uses" section should read: "For prevention of heartburn associated with acid [REDACTED] each brought on by eating or drinking certain food and [REDACTED] for consistency with other acid reducer products, the [REDACTED] and "prevention" should be removed.

- c. Directions, (bullets 2 and 3). Based on the protocol for Study No. 143-09-11255 and the actual study, the suspension is to be taken with 240 mL of water. Thus, the phrase "with a glass of water" needs to be included in the directions. Therefore, for consistency with Study No. 143-09-11255 and with Tagamet HB 200 tablet products and other products in this drug class, the directions should read (see prototype label, attachment 14.):

[REDACTED]

DRAFT LABELING

- d. Directions, bullet 4. The parenthetical statement [REDACTED] (hours)" does not accurately convey to the consumer that the dosage is limited to two 4 teaspoons doses or two 20 mL doses (taken in dose cup provided) in 24 hours. This statement is misleading and should be revised. The phrase "up to 8 teaspoons in 24 hours" suggests effectiveness for any dosage from 1 teaspoon up to 8 teaspoons taken at any time interval in 24 hours. Therefore, for accuracy and clarity the statement should be revised as follows: [REDACTED]

- e. Directions, bullet 5 (Attachment 3). The Agency has concerns about the potential of Tagamet HB 200 Suspension being administered to children. Consistent with the prototype labeling directions for products of this class, the directions state for the product [REDACTED]

The phrase [REDACTED] implies that it can be used in children. If data is not available to support the safety and effectiveness for this age group, even if a doctor tells you to use the product, then the label should state that the product should not be used in children under 12 years of age as an absolute. The

[REDACTED] DRAFT LABELING

- f. The Tamper Resistant/Tamper Evident Statement. The word "[REDACTED]" should be replaced with the word "[REDACTED]". Thus, the Tamper Resistant/Tamper

[REDACTED] DRAFT LABELING

- g. [REDACTED]
- 3. Inside of Opened Back Label (Attachment 4).

- a. Drug Interaction Warning. Some of the information included under the heading

[REDACTED] DRAFT LABELING

- b. Other information, bullet. For consistency with the Office of New Drug Chemistry (ONDC), the storage statement should read: "Store between 20° - 25°C (68° - 77°F).

- c. Response Rate Graphs, under heading "Clinically Proven", first sentence. The sentence needs to be revised to indicate that the clinical studies were done using the Tagamet HB 200 tablet and not the suspension (liquid dosage form). The same information appears in the Tagamet HB 200 tablet labeling. Because bioequivalence is shown between the Tagamet HB 200 tablet and the Tagamet HB 200 suspension, the Tagamet HB 200 tablet clinical data can also be used to support the Tagamet HB 200 suspension labeling. However, the consumer must be told which product was used in the studies. Therefore, the sentence should be revised as follows:

[REDACTED]

- d. Response Rate Graphs, bar graphs titles. For clarity for consumers, the word "tablet" should follow the term "Tagamet HB 200" under the bar graphs to read "Tagamet HB 200 Tablet."

- 4. Expiration Date/Lot Number. The location of the expiration date and lot number needs to be identified in accordance with § 201.17 for the 12 FL OZ bottle.

B. BOTTLE, Liquid 2 FL OZ Trial and 2 OZ Sample. (All recommendations refer to both the 2 FL OZ trial and sample sizes, unless otherwise noted.)

1. Front (Attachments 5 and 9).

a. Revisions should be made as recommended above for the 12 FL OZ. See I.A.1.a., b. and c., above.

2. Back.

a. Active Ingredient (Attachments 7 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.a., above.

b. Uses. (Attachments 7 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.b., above.

c. Directions, bullets 2 and 3 (Attachments 8 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.c., above. Note: If a dose cup is not provided then the statements should read:



d. Directions, bullet 4 (Attachments 8 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.d., above.

e. Directions, bullet 5 (Attachments 8 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.e., above.

f. Other Information (Attachments 8 and 12).

For consistency with the ONDC, the storage statement should read:



g. The Tamper Resistant/Tamper Evident Statement (Attachments 7 and 12). Revisions should be made as recommended above for the 12 FL OZ. See I.A.2.f., above. Note that the Tamper Resistant/Tamper Evident Statement statement follows "Uses" on 2 FL OZ trial and "Directions" on the 2 FL OZ sample bottles.

h. Response Rate Graphs, 2 FL OZ trial size (Attachment 8). The phrase [redacted] should be inserted as the heading for the response rate graphs to be consistent with the 12 FL OZ graphs. Note that the 2 FL OZ sample labeling does not include the response rate graphs. The response rate graphs should be included and revisions to this section should be made as recommended in I.A.3.c. and d, above.

i. Drug Interaction Warning (Attachments 8 and 11). Revisions should be made as recommended for the 12 FL OZ. See I.A.3.a., above.

3. Expiration Date/Lot Number. The location of the expiration date and lot number needs to be identified in accordance with § 201.17 for the 2 FL OZ Trial and the 2 FL OZ sample size bottles.

4. Although not a requirement a section titled "Tips for Managing Heartburn" should be included in the labeling. See the prototype label, Attachment 14.

II. Recommendations

- A. Before this application can be approved, the recommendations in I.A. and B., above, must be conveyed to the sponsor.
- B. The sponsor should be made aware that when the proposed Labeling Requirements for OTC Drug Products is finalized, the continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information. The labeling information is presented in the following specific order (in both upper and lowercase letters): **Active Ingredient(s), Purpose(s), Uses(s), Warnings, Directions, Other Information, and Inactive Ingredients.** No other information should precede the "Active Ingredient" section. Additional format and wording changes from the currently approved label are included in the prototype label. Further, because the Tagamet HB 200 suspension product has no outside container or wrapper and the labeling information appears on more than one panel, the sponsor should indicate the next page by using a word or a visual graphic (e.g., an arrow) to signal the continuation of the information to the next adjacent panel.

[Redacted Signature]

Mary S. Robinson, M.S.
Regulatory Review Chemist, HFD-560

[Redacted Signature]

Helen Cothran, B.S.
Team Leader, HFD-560

[Redacted Signature]

Rosemarie Neuner, M.D., M.P.H.
Medical Officer, HFD-560

[Redacted Signature]

Linda M. Katz, M.D., M.P.H. *K/26/98*
Deputy Director, HFD-560

APPEARS THIS WAY ON ORIGINAL

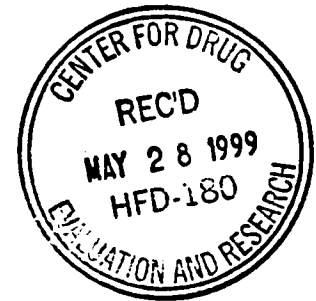
**14 Pages Redacted
Draft Labeling**

DUPLICATE
SmithKline Beecham
Consumer Healthcare

May 27, 1999

NDA 20-951
Non-Prescription Cimetidine Suspension 1%

Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-180)
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857



Re: Tagamet HB 200[®] Suspension Revised Draft Labeling: Drug Facts

Dear Dr. Talarico,

Please refer to our approvable New Drug Application 20-951 for Nonprescription Tagamet HB 200[®] (cimetidine) Suspension and to Ms. Kucuba's verbal request for revised product labeling in Drug Facts format.

Submitted herewith is revised draft labeling to replace that previously provided to the Agency on January 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 on pack.

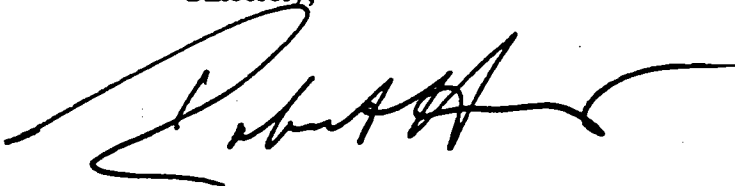
At Ms. Kucuba's request of 14 May 1999, the back labels for the retail (2 fl. oz. and 12 fl. oz. bottles) and sample (2 fl. oz. bottle) pack sizes were revised to comply with the March 17, 1999, Final Rule (64 FR 13254, OTC Human Drugs; Labeling Requirements). Please note that the small package labeling provisions as described in the Final Rule were applied to both the 2 oz. retail and 2 oz. sample size bottles.

We have also revised the front label of all proposed pack sizes to accommodate a color change in the [REDACTED]. This was the only change made to the front label that differs from the labeling submitted on January 8, 1999 for Nonprescription Tagamet HB 200[®] Suspension.

Letter to Dr. Talarico – NDA 20-951
May 27, 1999
Page 2 of 2

If you have any questions or comments concerning this matter, please do not hesitate to contact me at (973) 889-2513 or Sue James at (973) 889-2561.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert Harris", with a large, sweeping flourish extending to the right.

Robert Harris
Senior Regulatory Affairs Specialist
SmithKline Beecham Consumer Healthcare

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Encl. FDA Form 356h
Revised draft labeling for 12-ounce size container
Revised draft labeling for 2-ounce trial and sample size containers

Trade Name: Tagamet HB 200 Suspension 200 mg/mL

Generic Name: cimetidine

Applicant Name: SmithKline Beecham Consumer Healthare

HFD # 180

Approval Date If Known: July __, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO / ___ /

b) Is it an effectiveness supplement?

YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The study included in NDA 20-951 was a PK study with 26 healthy male subjects (mean age of 38), comparing OTC Tagamet tabs to the new OTC Tagamet suspension.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

 NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # . Drug Name .

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

- NDA# 17-920, Tagamet Tabs
- NDA# 17-920, Tagamet Liquid
- NDA# 17-939, Tagamet Injection
- NDA# 19-434, Tagamet Pre-Mixed Injection
- NDA# 20-238, Tagamet Tabs OTC
- NDA# 20-473, Tagamet Tabs OTC

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__ / NO /__ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / ___ /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.