CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20520, S001

Trade Name: ZANTAC 75 TABLETS, 75 MG

Generic Name: RANITIDINE HYDROCHLORIDE

Sponsor: GLAXOWELLCOME, INC.

Approval Date: 06/08/98

INDICATION(s): FOR THE PREVENTION OF MEAL-INDUCED HEARTBURN AT A DOSE OF 75 MG TAKEN 30 TO 60 MINUTES PRIOR TO A MEAL.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20520, S001

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20520, S001

APPROVAL LETTER

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 208

NDA 20-520/S-001

GlaxoWellcome, Inc
Attention: Thomas A. Gerding
Five Moore Drive
P.O. Box 13358
Research Triangle Park, NC 27709

JUN 8 1998

Dear Mr. Gerding:

Please refer to your supplemental new drug application dated November 5, 1996, received November 6, 1996 , submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Non-Prescription Zantac® 75 (ranitidine hydrochloride) Tablets, 75 mg.

We acknowledge receipt of your submissions dated December 5, 1997, March 31, and June 3, 1998. Your submission of December 5, 1997, constituted a complete response to our November 5, 1997, action letter. The current User Fee goal date for this application is June 8, 1998.

This supplemental new drug application provides for a new indication for the prevention of meal-induced heartburn at a dose of 75 mg taken 30 to 60 minutes prior to a meal.

We have completed the review of this supplemental new drug application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text that was submitted on March 31, 1998. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling dated March 31, 1998. Marketing of the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-520/S-001. Approval of this submission by FDA is not required before the labeling is used.

As stated in your letter dated June 8, 1998, you agreed to revise the labeling for this drug product within 6 months or at the next printing, whichever comes first, as follows:

1. For consumer readability, the Tamper Resistant/Tamper Evident statement on the side panel of the carton, the back of the package insert, and wherever the statement appears on the labeling, will be changed from all upper case to upper and lower case to read: "Do not use if

the individual blister unit is open or torn."

2. Under the "**Warnings**" section on the back panel of the carton, an allergy warning will be added. We suggest the following: "**Allergy Warning**: Do not use if you are allergic to Zantac (ranitidine hydrochloride) or other acid reducers." To avoid unintentional over-medicating by consumers, the following warning will be added: "**Do Not Use** with other acid reducers." In accordance with the new labeling format for OTC drug products under "**Do Not Use**", these statements will be bulleted warnings. Also, you are considering incorporating these warnings in the package insert..

3. The "**Uses**" section will be revised to denote "heartburn" as the primary symptom, with the other symptoms as secondary symptoms. The "**Uses**" section will read: "For relief of heartburn associated with acid indigestion and sour stomach," and "For prevention of heartburn associated with acid indigestion and sour stomach brought on by certain food and beverages."

4. The "pregnancy-nursing warning" on the back panel of carton will be revised to come right before the "**Keep out of reach. . .**" warning statement.

5. The phrase "**30 to 60 minutes before eating a meal you expect to cause symptoms**" under "**Directions.**" is bolded. To be consistent with other acid reducer products, in the prevention phrase under the "**Directions**" section on the back panel of the carton and on the front of the package insert, only the word/phrase: "**prevention**" and "**30 to 60 minutes before**" will be bolded. This "**Directions**" statement, therefore, will appear as "To **prevent** symptoms, swallow 1 tablet with a glass of water **30 to 60 minutes before** eating food or drinking beverages that cause heartburn."

6. For consistency with other acid reducer drug products, under the "For relief of" and the "For the Prevention of" "**Directions**", the phrase "a glass of" will be inserted between the words "with" and "water" to read: "swallow 1 tablet with a glass of water." We believe that the use of a "glass" of water is appropriate to increase the likelihood that an adequate volume of fluid is ingested to ensure proper esophageal transit, disintegration and dissolution of the medication.

7. In the prevention phrase under "**Directions**" on the back panel of the carton and on the front of the package insert under " How should I take Zantac 75?" the phrase "brought on by consuming food and beverages" is not needed and will be deleted. This information is in the "**Uses**" section.

8. The "Tips for Managing Heartburn" section should be revised to be consistent with other drug products of this class.

Tips for Managing Heartburn

- Do not lie flat or bend over soon after eating
- Do not eat late at night, or just before bedtime
- Certain foods or drinks are more likely to cause heartburn, such as, rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, even some fruits and vegetables
- Eat slowly and do not eat big meals
- If you are overweight, lose weight
- If you smoke, quit smoking
- Raise the head of your bed
- Wear loose fitting clothing around your stomach

These "Tips" above preferably should be included in the carton label; however, if space is at a premium, they may be included in the package insert.

In addition to the revisions specified above, we suggest that you revise the labeling, at your earliest convenience, so that it is in compliance with the February 27, 1997, Proposed Labeling Requirements for OTC Drug Products. For example, the labeling information headings are presented with the first letter of the heading in upper case. followed by lower case letters and in the following specific order. **Active Ingredient(s), purpose(s), Use(s), Warning(s), Direction(s), Other Information and Inactive Ingredients.** No other information should precede the "**Active Ingredient(s)**" section. Please note that the Proposed Labeling Requirements for OTC Drug Products is subject to change pending publication of the final rule. Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

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

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

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane, Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Albert Rothschild, at (301) 827-2222.

Sincerely yours,

/S/ 6-5-98

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

/S/ for 6-18-98

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

APPEARS THIS WAY
ON ORIGINAL

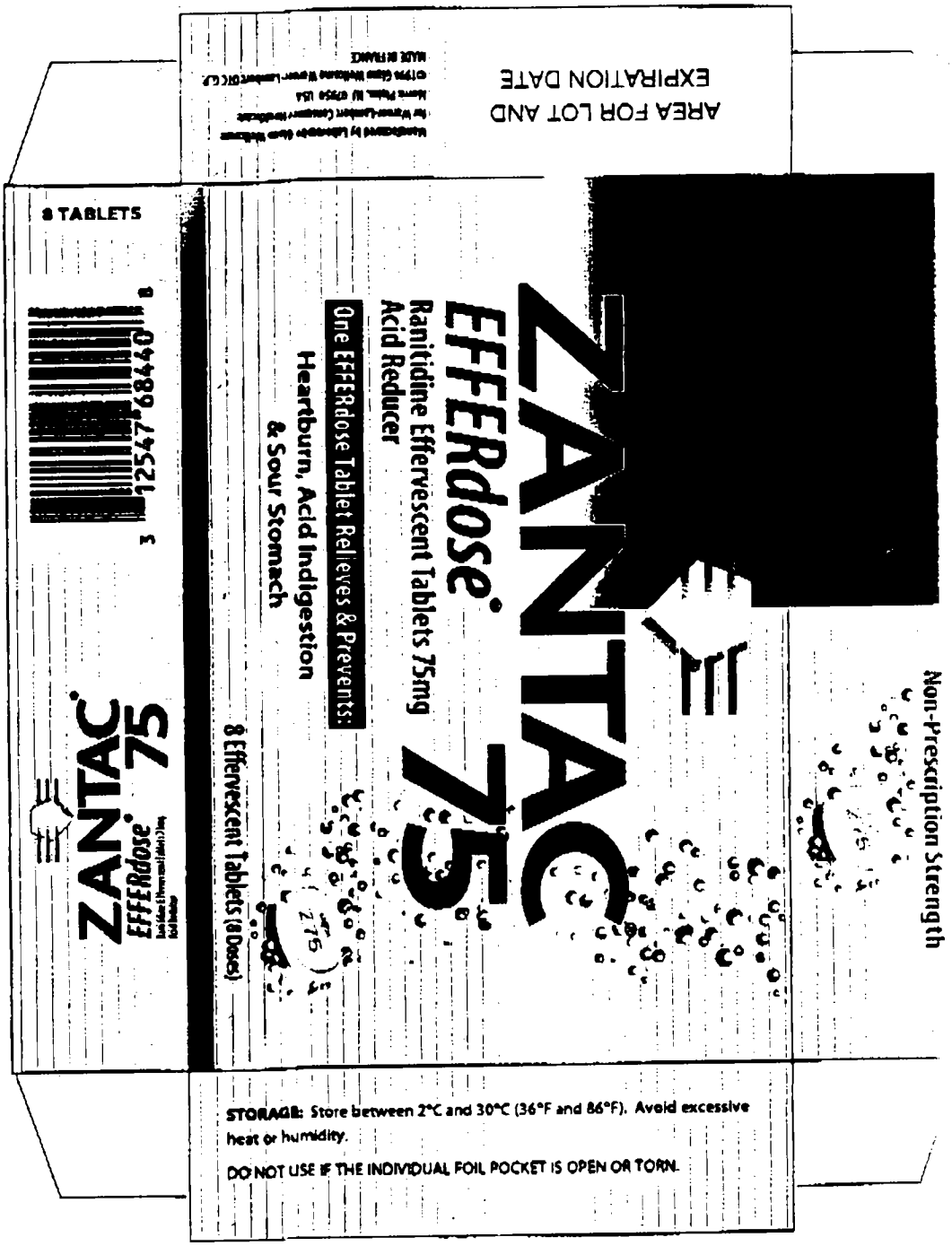
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20520, S001

PRINTED LABELING

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL



APPEARS THIS WAY
ON ORIGINAL

20-745/S-001

ZANTAC
EFFERdose® 75

ACTIVE INGREDIENT

Each tablet contains: 84 mg ranitidine hydrochloride (equivalent to 75 mg ranitidine)

USES

- For the relief of Heartburn, Acid Indigestion and Sour Stomach.
- For the prevention of Heartburn, Acid Indigestion and Sour Stomach brought on by consuming food and beverages.

DIRECTIONS

- Dissolve 1 EFFERdose tablet completely in a full glass of water. (Do not swallow or chew the tablet. Do not store the solution for future use).
- For the relief of symptoms, drink the entire amount of solution.
- For the prevention of symptoms brought on by consuming food and beverages, drink the entire amount of solution 30 to 60 minutes before eating a meal you expect to cause symptoms.
- Can be used up to twice daily (up to 2 EFFERdose tablets in 24 hours)
- This product should not be given to children under 12 years old unless directed by a doctor.

READ THE LABEL

- Read the directions, consumer information leaflet and warnings before use.
- Keep the carton. It contains important information.

WARNINGS

- Do not take the maximum daily dose for more than 14 consecutive days, unless directed by your doctor.
- As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
- If you have trouble swallowing or persistent abdominal pain, see your doctor promptly. You may have a serious condition that may need different treatment.
- Keep this and all drugs out of the reach of children.
- In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
- Do not use this product if you are on a sodium restricted diet unless directed by a doctor.
- Phenylketonurics: Contains Phenylalanine 0.4 mg Per Tablet.

INACTIVE INGREDIENTS

Aspartame, monosodium citrate anhydrous, povidone K-30, sodium bicarbonate and sodium benzoate.
Sodium content: 95 mg per tablet

Questions or Comments?

Call us toll-free at
1-800-223-0182

What you should know about

ZANTAC® EFFERdose® 75

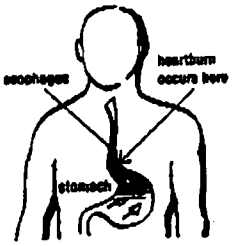
Ranitidine Effervescent Tablets 75 mg
Acid Reducer

(Please read all of this information before taking Zantac 75 EFFERdose. Save this leaflet for future reference.)

What is Zantac 75 EFFERdose?

- Zantac 75 EFFERdose is an effervescent tablet containing 75 mg of ranitidine (as ranitidine hydrochloride, 84 mg), a medicine that doctors have prescribed more than 200 million times worldwide. One EFFERdose tablet dissolves in water into a clear liquid.
- Prescription strength Zantac has an excellent safety record and the active ingredient in Zantac 75 EFFERdose has been taken safely with many frequently prescribed medications.
- Zantac 75 EFFERdose is sugar free.
- Zantac 75 EFFERdose is an alternate choice for people who prefer a liquid medication, but enjoy the convenience of traveling with a tablet.

What symptoms does Zantac 75 EFFERdose treat?



Zantac 75 EFFERdose relieves and prevents heartburn, acid indigestion and sour stomach.

Certain foods and drinks, and even lying down to sleep, can cause heartburn, acid indigestion or sour stomach. It is normal for the stomach to produce acid, especially after consuming food and beverages. However, acid in the wrong place, such as the esophagus, or too much acid, can cause burning pain and discomfort.

How should I take Zantac 75 EFFERdose?

Adults and children 12 years of age and older: Dissolve 1 EFFERdose tablet completely in a full glass of water. (Do not swallow or chew the tablet. Do not store the solution for future use.)

- For **relief** of heartburn, acid indigestion and sour stomach, drink the entire amount of solution.
- For **prevention** of symptoms brought on by consuming food and beverages, drink the entire amount of solution **30 to 60 minutes before eating a meal you expect to cause symptoms.**

This medication can be used up to twice daily (2 tablets in a 24-hour period). This product should not be given to children under 12 years old unless directed by a doctor.

How does Zantac 75 EFFERdose work?

Zantac 75 EFFERdose reduces the production of stomach acid. This is what makes Zantac 75 EFFERdose different from antacids, which neutralize the acid already in your stomach. Antacids do not reduce the production of acid.

Tips for managing heartburn

- Do not lie flat or bend over soon after eating.
- Do not eat late at night, or just before bedtime.
- Avoid foods or drinks that are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fruits and vegetables.
- Eat slowly and do not eat big meals.
- If you are overweight, lose weight.
- If you smoke, stop or cut down smoking.
- Raise the head of your bed.
- Avoid wearing tight clothing around your stomach.

83.6mm

fold lines

FRONT

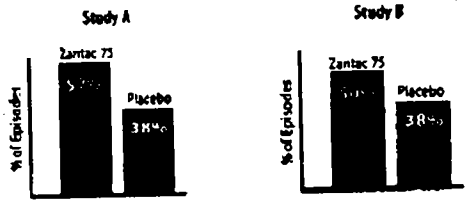
20-745/S001

15mm

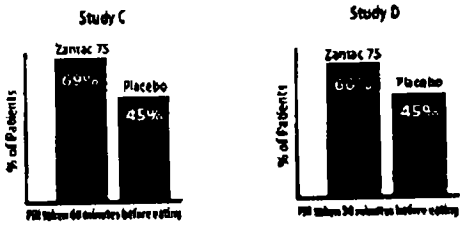
Clinical studies prove Zantac 75 is effective in relieving...

In clinical studies using Zantac 75mg Tablets (of which Zantac 75 EFFERdose is equivalent) Zantac 75 was significantly better than placebo pills in relieving and preventing heartburn.

Percent of Heartburn Episodes Relieved



Percent of Patients with Prevention or Reduction of Heartburn Symptoms



...and preventing heartburn

When should I see a doctor?

- Many people do get heartburn, acid indigestion and sour stomach. However, if you have abdominal pain that won't go away, or you have trouble swallowing, consult your doctor promptly. You may have a serious condition that may need a different treatment.
- As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
- In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

What other things should I be concerned about?

- Do not take Zantac 75 EFFERdose more than two times per day (maximum daily dosage) for more than 14 days in a row (2 weeks) unless your doctor tells you to do so.
- Keep this and all drugs out of the reach of children.
- Do not use this product if you are on a sodium-restricted diet unless directed by a doctor.
- **Phenylketonurics: Contains Phenylalanine 8.4 mg Per Tablet**

IF YOU HAVE ANY QUESTIONS ABOUT ZANTAC 75 EFFERDOSE, CALL US TOLL FREE AT 1-800-223-0182 WEEKDAYS BETWEEN 9:00 am AND 5:00 pm EST, OR WRITE US AT:

CONSUMER AFFAIRS
WARNER-LAMBERT CONSUMER HEALTHCARE
182 TABOR ROAD
MORRIS PLAINS, NJ 07950

Zantac is a registered trademark of the Glaxo Wellcome group of companies

DO NOT USE IF THE INDIVIDUAL FOIL POCKET IS OPEN OR TORN.

Manufactured by Laboratoire Glaxo Wellcome
for Warner-Lambert Consumer Healthcare
Morris Plains, NJ 07950 USA

MADE IN FRANCE

APPEARS THIS WAY ON ORIGINAL

BACK

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20520, S001

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S CONSULT REVIEW

NDA:	20-745 (SE1)(001) JUN - 1 1998
Sponsor:	GlaxoWellcome, Inc.
Drug name:	Zantac (ranitidine hydrochloride) 75EFFERdose Tablets for Over-the-Counter Use
Date submitted:	May 12, 1998
Date received:	May 13, 1998
Date received by Medical Officer:	May 21, 1998 JUN 2[illegible] 1998
Review completed:	May 28, 1998 /S/
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Zantac 75 EFFERdose Tablets was approved on February 26, 1998, based on demonstration of bioequivalence to Zantac 75 Tablets, for treatment of heartburn, acid indigestion and sour stomach.

On November 5, 1997 the sponsor was issued an approvable letter for Zantac 75 Tablets for prevention of heartburn (on the basis of clinical efficacy studies). The sponsor states that final labeling revisions for that indication are currently under review.

The current submission is a supplemental application containing revised draft labeling and proposing "revision of the Zantac 75 EFFERdose labeling to be identical in content (in terms of the prevention indication) to the labeling currently undergoing final review for Zantac 75 Tablets." The sponsor indicates that this would ensure consistency in labeling across line extensions. I have reviewed this submission only with regard to the requested revision of the the indications.

Reviewer's Comments and Discussion:
Because Zantac EFFERdose was approved on the basis of establishing bioequivalence to Zantac 75, the indications for both products should be the same and the labeling for the two products should be identical, except for information having to do with the dosage form. Accordingly, when and if Zantac 75 is approved for prevention of heartburn, this indication also should be reflected in the Zantac EFFERdose labeling.

Note, however, that while Zantac EFFERdose and Zantac 75 are bioequivalent with regard to ranitidine, there still may be some minor difference in the effect of the two products on gastric pH because of the bicarbonate content of the effervescent (EFFERdose) formulation. As described in my review of this NDA dated March 7, 1997 (pages 2 and 3), the sodium

bicarbonate in the effervescent formulation contributes about 1.6mEq acid neutralizing capacity (ANC) per dose, which is well under the 5mEq ANC stipulated for including a product in the antacid OTC monograph.

In a pharmacodynamic study designed to compare the effect of 300mg of the Zantac EFFERdose 150mg formulation (6.4mEq ANC; [6.4-8.2mEq, based on the abstract submitted by the sponsor]) with that of 300mg of Zantac tablet formulation on gastric pH, it was found that over a 23 hour period there was no significant difference in gastric pH or gastric acid content. However, there was in the first hour after dosing a significantly higher gastric pH following Zantac EFFERdose than following Zantac Tablets (mean median pH of 2.39 with the effervescent formulation as compared to 1.25 for the standard tablet). No similar study has been done with Zantac 75 EFFERdose. In studies where intragastric pH is has been used as a predictor or correlate of effectiveness of therapies in treating acid-related disorders, a gastric pH of 4 or above has been the usual target. On the basis of this information, I would expect any antacid contribution of sodium bicarbonate to the efficacy of Zantac 75 EFFERdose for the treatment of heartburn to be minimal. Thus, the effectiveness claims for Zantac 75 EFFERdose should be identical to those for Zantac 75.

Conclusions and Recommendations:

The indications for Zantac EFFERdose should be identical to those for Zantac 75 and the labeling for the two products should be the same except for information related to the dosage form.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 5/28/98

cc:
NDA 20-745
HFD-180
HFD-180/LTalarico /S/ 6-1-98
HFD-180/KRobie-Suh
HFD-180/MFolkendt
HFD-560/DBowen
HFD-560/LKatz
HFD-560/ARothschild
f/t 5/28/98 krs
MED\N\20745805.0KR

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20520, S001

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20745	**Trade Name:**	ZANTAC 75 EFFERDOSE TABS
Supplement Number:	1	**Generic Name:**	RANITIDINE HCL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	PN	**Proposed Indication:**	Prevention of heartburn, acid indigestion, and sour stomach (30-60 minutes prior to meal)

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Status
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Label states that product should not be given to children under 12 unless directed by a doctor. 02/224/99)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ALBERT ROTHSCHILD

/S/
Signature

2/24/95
Date

EXCLUSIVITY SUMMARY FOR NDA # 20-745 SUPPL #S-001

Trade Name: Zantac Generic Name: Ranitidne

Applicant Name: GlaxoWellcom, Inc HFD # 560

Approval Date If Known : March , 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 /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /X/ NO /_ _/

If yes, what type? (SE1, SE2, etc.) _SE1

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.

_____

_____

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:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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# _____ _____

NDA# _____ _____

NDA# _____ _____

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.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 2/24/99

Signature Date

Title: OC Pdn Analyst.

/S/ 3/22/99

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

HFD-560
DESK-Rothschil

GlaxoWellcome

May 12, 1998

Deborah L. Bowen, M.D., Director
Division of Over the Counter Drug Products
Center for Drug Evaluation and Research
HFD-560, Room S205
Food and Drug Administration
Corporate 2
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-745; Zantac® (ranitidine hydrochloride) 75 EFFERdose® Tablets for Over-the-Counter Use
Supplemental Application: Labeling

Dear Dr. Bowen:

Reference is made to the New Drug Application identified above, which was approved on February 26, 1997. Please also refer to NDA 20-520, S-001 for Zantac 75 Tablets. Supplement 001, submitted on November 5, 1996, provides for the use of Zantac 75 for the prevention of meal-induced heartburn. An approvable letter for this supplement was issued on November 5, 1997, and final labeling revisions are currently under review.

Because Zantac 75 EFFERdose Tablets are bioequivalent to Zantac 75 Tablets, we would like to gain approval to include the prevention labeling on the EFFERdose label upon approval of NDA 20-520, S-001. To this end, we are submitting a supplemental application to revise the Zantac 75 EFFERdose labeling to be identical in content (in terms of the prevention indication) to the labeling currently undergoing final review for Zantac 75 Tablets. This will ensure consistency in labeling across line extensions.

In addition, the approval letter for Zantac 75 EFFERdose tablets requested revisions to the draft labeling (these revisions were previously agreed between representatives of the Agency and Glaxo Wellcome). We have incorporated these revisions into the enclosed draft labeling.

For your convenience, the revisions to the Zantac 75 EFFERdose labeling are outlined below.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

Revisions Requested in February 26, 1998 Approval Letter

- Delete the word [redacted] from the second sentence of the first bullet statement on the front of the package insert.
- Revise the directions to state [redacted]
- Add a section titled [redacted] with the following bullet statements to the package insert:

[redacted]

Revisions Based on NDA 20-520, S-001

Package Insert:

- Under "What symptoms does Zantac 75 EFFERdose treat?", added the following underlined text: [redacted]
- Under "How should I take Zantac 75 EFFERdose?", added the following as a bullet point: [redacted]
- Added a sidebar titled [redacted] which includes a graphical representation of the clinical study data forming the basis of the prevention indication.

Carton Label:

- On the front of the carton, added the following underlined text:
- Under "Uses", added a second bullet point:
- Under "Directions", added the following as a bullet point

In a May 5, 1998 telephone conversation between Ms. Sara Armentrout of Glaxo Wellcome and Mr. Al Rothschild of DODP, a tentative agreement was reached that this supplement could be submitted in advance of approval of NDA 20-510, S-001, with the intention of concurrent final review of both applications. Following a facsimile transmission of this request from Glaxo Wellcome, and a subsequent telephone conversation with the Agency on May 7, 1998, it was agreed that this submission could proceed.

Four copies of the draft labeling (full-color mechanicals) are included with this submission. In addition, a complete copy of this submission is being provided directly to Mr. Rothschild as a Desk Copy.

We appreciate your willingness to expeditiously receive and review this supplemental application in order to ensure consistency of labeling between our two Zantac 75 line extensions. Please contact Sara Armentrout, Associate Director, OTC Regulatory Affairs at (919) 483-5140 if you have any questions regarding this submission or require additional information.

Sincerely,

Thomas A. Gerding

Thomas A. Gerding
Director, Regulatory Affairs
International OTC Development

Warner-Lambert Company
170 Tabor Road
Morris Plains, New Jersey 07950
973 540-5331
Fax: 973 540-4300
E-Mail: judi.sills@wl.com

Judith M. Sills, Pharm.D.
Senior Director
U.S. Regulatory Affairs and Global Product Safety
Consumer Healthcare Research & Development

WARNER LAMBERT

March 3, 1999

Debra Bowen, M.D., Director
Division of Over the Counter Drug Products
Center for Drug Evaluation and Research
HFD-560, Room S205
Food and Drug Administration
Corporate 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-745/S-001; ZANTAC® (ranitidine hydrochloride) 75 EFFERdose® Tablets for Over-the-Counter use.

Dear Dr. Bowen:

Reference is made to our approved New Drug Application for Zantac® (ranitidine hydrochloride) 75 EFFERdose® Tablets for Over-the-Counter use, NDA 20-745 and to our pending supplemental application for the prevention of meal-induced heartburn, S-001, submitted on May 12, 1998.

In a March 1, 1999 telephone conversation between Ms. Martha Propsner of Warner-Lambert and Mr. Al Rothschild of the Division, followed by a telefax correspondence from the Division, Mr. Rothschild requested that Warner-Lambert provide a written commitment to make the following labeling revisions before the product is marketed with the new indication:

- Under the "**Warnings**" section of all labeling, add the following statement as the first bulleted warning:
- Under the "**Warnings**" section of all labeling, add the following additional bulleted warning:

This letter constitutes our written commitment to make the above labeling revisions before ZANTAC® (ranitidine hydrochloride) 75 EFFERdose® Tablets for Over-the-Counter use is marketed with the prevention of meal-induced heartburn indication.

A copy of this letter is being transmitted via telefax directly to Mr. Rothschild. Please feel free to contact the undersigned at (973) 540-5331 if there are any questions concerning this submission.

Please be advised that certain information contained in this submission is confidential and should, therefore, be exempt from disclosure under the Freedom of Information Act or otherwise. I request that you notify the undersigned not less than three business days prior to any contemplated disclosures of any or all of this material by FDA.

Sincerely,

Hans F. Knapp for

Judith M. Sills, Pharm. D.
Senior Director
US Regulatory Affairs and
Global Product Safety

APPEARS THIS WAY
ON ORIGINAL

Division of OTC Drug Products
Labeling Review

NDA No. 20-745/SE1-001

TYPE OF SUBMISSION:	Supplemental Application: New Labeling Indication for the Prevention of Meal-Induced Heartburn and Labeling Revisions in Response to FDA Approval Letter
SPONSOR:	GlaxoWellcome, Inc.
DRUG PRODUCT:	Zantac 75 EFFERdose® Tablets
INDICATIONS:	For the relief of heartburn, acid indigestion and sour stomach For the prevention of heartburn, acid indigestion and sour stomach brought on by consuming food and beverages
ACTIVE INGREDIENT:	Ranitidine 75 mg per effervescent tablet
SUBMISSION DATE:	May 12, 1998
REVIEWER:	Gloria Chang
REVIEW DATE:	1/4/99
PROJECT MANAGER:	Al Rothschild

Background:
NDA 20-745 for Zantac 75 EFFERdose tablets (effervescent tablet dosage form) was approved for OTC use on February 26, 1998 for the relief of heartburn, acid indigestion and sour stomach (Attachment 1). GlaxoWellcome submitted this supplemental application (Attachment 2) to revise the Zantac 75 Efferdose® tablet labeling to include the indication for the prevention of meal-induced heartburn to be consistent with the approved indications for Zantac 75 tablets (NDA 20-520/S-001). This submission also includes the requested labeling revisions in the Agency's approval letter of February 26, 1998.

A. Reviewer's comments on changes made in response to the February 26, 1998 approval letter

1. On the front of the package insert, first bullet, second sentence, in the section "What is Zantac 75 EFFERdose?", the word [redacted] was deleted and the sentence now reads [redacted] This change is acceptable.

2. The Directions were revised to state [redacted] This change is acceptable at this time.

3. The section [redacted] was added to the package insert. The bulleted statements should be revised to reflect the latest revisions as follows:

Original Review
to Docket Room
2/1/99 /S/

a) The third bullet should be changed to read:

b) The sixth bullet should be changed to read:

c) The eighth bullet should be changed to read:

B. Reviewer's comments on labeling changes subsequent to the February 26, 1998 approval letter and other comments

1. Carton (Front Panel). The text was revised to read: "One EFFERdose Tablet Relieves & Prevents:" This is acceptable.

2. Carton (Back Panel).

a. **Uses** Section

(i) A second bullet was added to read: For consistency with other acid reducers, the bolding of the words needs to be removed and the sponsor needs to use lower case for in both the and the

(ii) The sponsor should consider revising the text and format in the **Uses and Directions** section to reflect the proposed draft prototype label (Attachment 3). We also suggest that the sponsor consider the labeling headings and subheadings format and use of upper and lower case letters as proposed in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products (62 FR 9024).

(iii) For consistency with other acid reducers and the draft prototype label, the word should be replaced with and the word should be added to this clause as follows:

(iv) The **Uses** section should be revised to denote as the primary symptom, with the other symptoms as secondary symptoms to read:

b. **Directions** section

(i) Change the phrase _____ to read _____ respectively and bold only the terms _____

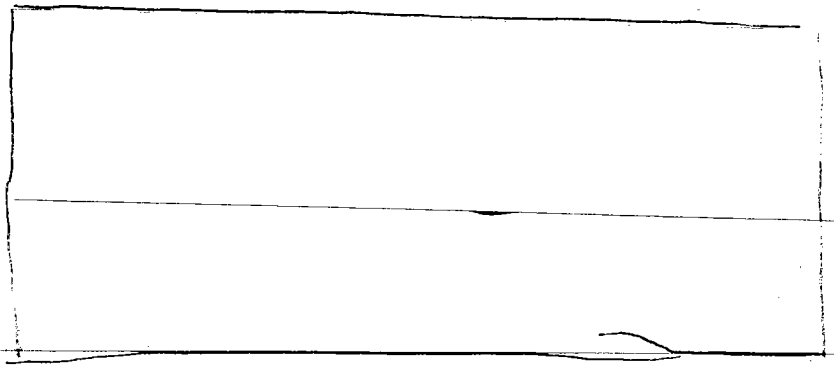
(ii) Replace the term _____ with the term _____ in both the _____ directions to be consistent with the first bulleted statement in the package insert (consumer information leaflet) (front panel) that states "One EFFERdose tablet dissolves in water into a clear liquid."

(iii) To ensure that the consumer understands that the entire amount of the "liquid" needs to be taken shortly after dissolution, revise the phrase _____ directions to read _____

(iv) Delete the phrase _____ This phrase is redundant and unnecessary since it is stated in the **Uses** section.

(v) Although not stated in the 2/26/98 approval letter for the EFFERdose tablets, we believe that for consumer safety, the phrase _____ should be bolded and listed as the first bulleted statement under **Directions**.

(vi) In adding the prevention directions to the labeling, the sponsor has used a combination of labeling approved in NDA 20-520/S-001 (Zantac 75 tablets) and NDA 20-745 (Zantac 75 EFFERdose). We believe that the sponsor's directions should be simplified and made clearer to consumers. Based on the above, and for consistency with other acid reducers and the labeling format of Zantac 75 tablets, we recommend that the first three bulleted statements in the **Directions** section be replaced with the following three revised bulleted statements.



c. **Warnings** section

(i) The sponsor needs to add as the first bulleted warning statement. The warning also needs to be added. (See Attachment 3.) These warnings should also be added to the package insert.

(ii) Move the **pregnancy** warning to come right before the **"Keep out of reach of children"** warning.

3. Carton (Side Panel)

a. Tamper Resistant/Tamper Evident statement:

(i) Because the individual foil pockets are labeled as the term should be changed to

(ii) For consumer readability, the Tamper Resistant/Tamper Evident statement needs to be in upper and lower case letters to read: This change is applicable wherever the Tamper Resistant/Tamper Evident statement appears on the labeling.

b. Storage Statement

(i) For consistency with the Office of New Drug Chemistry (ONDC) recommendations, the storage temperature should be changed to read At this time, we are allowing the statement for pouches or blister-type packs. For consistency with the prototype draft label and the February 27, 1997 proposed rule, the heading in the storage statement should be deleted. Also, the storage statement should be moved to the back panel of the carton under the **Other Information** section to read These storage statement changes are applicable wherever the statement appears in the labeling.

4. Package Insert (Consumer Information Leaflet)

a. Front Panel

(i) In the section statement titled: the bulleted statement that reads:

is misleading and not consumer friendly. It is the 150 to 300 mg strength of ranitidine that was prescribed, not the OTC 75 mg strength. Thus, the statement needs to be revised to read:

(ii) The sponsor needs to revise the titled section Zantac 75 EFFERdose relieve and prevent?" Under this section, the following text was revised to read:

To be consistent with the **Uses** section, we suggest that the statement be revised to read

(iii) In the section titled "How should I take Zantac 75 EFFERdose?" The relief and prevention directions should be revised as stated in the reviewer's comments under B.2.b.vi above.

(iv) The "READ THE LABEL" section on the back panel of carton advises consumers to read the Note that whether the term "consumer information leaflet" or "package insert" is used, the same term should be used consistently throughout the labeling. The sponsor should consider including the title "Consumer Information Leaflet" on the front panel of the package insert labeling to make it easier for the consumer to identify the leaflet.

b. Back Panel

(i) The sponsor has revised the side bar section title to reflect the prevention indication to read This is acceptable. To increase consumer's understanding of this section, the sponsor needs to revise the title over the graphical clinical studies section that reads to read:

(ii) In the graphical section titled "Percent of Patients with Prevention or Reduction of Heartburn Symptoms," the sponsor needs to change the term [redacted] in the statements under the prevention graphs. The statements should read [redacted]

(iii) In the section titled "What other things should I be concerned about?" the first bullet that reads [redacted] needs to be revised. For consistency with the prototype draft label and for consumer readability, the statement should read: [redacted]

(iv) For consumer readability, the Tamper Resistant/Tamper Evident statement needs to be in upper and lower case letters and revised to read: [redacted]

AGENCY RECOMMENDATIONS

I. The following modifications need to be made in order for this NDA supplement to be approved.

1. Under the **Warnings** section add the following warning as the first bulleted warning: [redacted] Also add the warning [redacted] (See Attachment 3.) These warnings should also be added to the package insert (consumer information leaflet).

II. The following labeling changes need to be made within 180 days or at the next printing, whichever comes first.

1. Under the **Uses** section of the carton back panel, remove the bolding of the words [redacted] from the [redacted] bulleted statements, respectively. Also, use lower case for [redacted] in both the [redacted]

2. Under the **Uses** section, revise the bulleted statements to denote "heartburn" as the primary symptom, with the other symptoms as secondary symptoms. The revised statements to read as follows:

3. Under the **Directions** section: (a) replace the phrase respectively. Bold only the terms "**relieve,**" "**prevent,**" and the phrase "**30 to 60 minutes before.**" (b) delete the phrase (See Attachment 3.) (c) replace the term (d) To ensure that the consumer understands that the entire amount of the "liquid" be added. (e) For safety reasons, we also recommend that the phrase be bolded and that the statement be moved as the first bulleted statement. (f) Based on the above, and for consistency with other acid reducers and the labeling format of Zantac 75 ~~ta~~blets, replace the first three bulleted statements of the **Directions** section and the two bulleted statements in the section of the front panel of the package insert titled "How should I take Zantac 75 EFFERdose?" with the following three revised bulleted statements:

4. Under the **Warnings** section, move the **pregnancy** warning to come right before the **"Keep out of reach of children"** warning.

5. In the Tamper Resistant/Tamper Evident statement on the carton and package insert replace the term and use upper and lower case letters to read

6. To be consistent with the Office of New Drug Chemistry (ONDC) recommendations, change the storage statement to read [redacted] Also, delete the heading **"STORAGE:"** and move the storage statement to the back panel of the carton under the **Other Information** section to read [redacted] These storage statement changes are applicable wherever the statement appears in the labeling.

7. In the front panel of the package insert (consumer information leaflet) titled: "What is Zantac 75 EFFERdose?" revise the bulleted statement that reads: [redacted] to read: [redacted]

8. In the front panel of the package insert, revise the title heading [redacted] to read [redacted] For consistency with the **Uses** section, revise the text that reads [redacted] to read [redacted]

9. In the package insert front panel under the bulleted section titled "Tips for Managing Heartburn," revise the bulleted statements to reflect the latest revisions (see Attachment 3) as follows:

a) The third bullet should be changed to read: [redacted]

b) The sixth bullet should be changed to read: [redacted]

c) The eighth bullet should be changed to read: [redacted]

10. In the package insert back panel, revise the title over the graphical clinical studies that reads

to read:

In the statements under the prevention graphs, replace the word with the word to read

11. In the section titled "What other things should I be concerned about?" on the back panel of the package insert, revise the first bulleted statement that reads

to read

III. The sponsor should be advised of the following.

1. The sponsor should consider revising the text and format of the labeling to reflect the proposed draft prototype label (Attachment 3). We also suggest that the sponsor consider the labeling headings and subheadings and use of upper and lower case letters as proposed in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products (62 FR 9024). Note that in the proposal, the heading "**Warnings**" precedes the "**Directions.**" The sponsor should be aware that the proposed rulemaking and the prototype label are subject to change pending the finalization of the proposed rule.

2. The sponsor should consider including the title "Consumer Information Leaflet" on the front panel of the package insert labeling to make it easier for the consumer to identify the leaflet. Note that whether the term "consumer information leaflet" or "package insert" is used, the same terms should be used consistently throughout the labeling.

/S/
Gloria Chang, R.Ph.
Interdisciplinary Scientist, HFD-560

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

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

/S/ 2/8/99
Linda M. Katz, M.D., M.P.H.
Deputy Director, HFD-560

Attachments