CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020745

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

M E M O R A N D U M

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

DATE: February 19, 1998

/S/ 2/19/98

FROM: Michael Folkendt
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Joseph Sieczkowski, Ph.D. /S/ 2-19-98
Review Chemist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Eric Duffy, Ph.D. /S/ 2/19/98
Chemistry Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Lilia Talarico, M.D. /S/ 2-19-98
Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: Debra Bowen, M.D.
Director
Division of Over-the-Counter Drug Products, HFD-560

Mailed 02/23/98

/S/

SUBJECT: Acid neutralizing capacity of Zantac® 75 EFFERdose® (ranitidine hydrochloride) Effervescent Tablets, 75 mg [NDA 20-745]

In response to your February 12, 1998 memorandum concerning the acid neutralizing capacity of 75 mg ranitidine hydrochloride effervescent tablets, we are attaching information contained in the application (NDA 20-251, volume 1, page 316-323) for the prescription Zantac® EFFERdose® (ranitidine hydrochloride) Effervescent Tablets, 150 mg.

This information summarizes the Preliminary Antacid Test (as outlined in former 21 CFR 331.25)* and the acid neutralizing capacity test (as outlined in former 21 CFR 331.26)* performed on 6 batches of 150 mg ranitidine hydrochloride effervescent tablets. The summary of the results from these tests for all six lots are as follows:

Regulatory Test	Test results for six lots of 150 mg effervescent tablet	minimum antacid specification
preliminary antacid test (as outlined in former 21 CFR 331.25)*		pH ≥3.5
Acid neutralizing capacity (as outlined in former 21 CFR 331.26)*	average ANC: 4.0 mEq	ANC ≥5 mEq

As indicated in the above table, the 150 mg ranitidine hydrochloride effervescent tablet does not meet either the former specification (for preliminary antacid test, pH ≥3.5; for Acid neutralizing capacity, ANC ≥5 mEq) or the current ANC specification under 21 CFR 331.10 of ANC ≥5 mEq.

Because the composition of the 75 mg ranitidine hydrochloride effervescent tablet is exactly half of that of the 150 mg tablet

it is reasonable to assume that the 75 mg ranitidine hydrochloride effervescent tablet also would not meet the regulatory specifications for an antacid.

APPEARS THIS WAY
ON ORIGINAL

* [The antacid regulation were revised on February 8, 1996 in 61 FR 4823.]

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-745
HFD-180/Div. Files

MEMORANDUM

APPEARS THIS WAY
ON ORIGINAL

HFD-180
M. Folkendt

Division of Over-the-Counter Drug Products
Labeling Review

NDA #: 20-745
TYPE OF SUBMISSION: Amendment to pending Application
SPONSOR: GlaxoWellcome Inc.
DRUG PRODUCT: Zantac 75® EFFERdose® Tablets
INDICATION: For relief of Heartburn, Acid Indigestion and Sour Stomach
ACTIVE INGREDIENT: Ranitidine hydrochloride effervescent tablets, 75 mg
SUBMISSION DATE: August 25, 1997
REVIEWER: Mary S. Robinson, M. S.
REVIEW DATE: January 12, 1998
PM: Sakineh Walthers

APPEARS THIS WAY ON ORIGINAL

Background:

This amendment to a pending application was filed as a 505(b)(1) submission in response to specified labeling changes requested by the agency in an approvable letter, dated July 8, 1997. The basis for the approval of the product is the demonstration of bioequivalence to Zantac 75 Tablets (NDA 20-520, approved December 19, 1995). The sponsor has submitted full color reproductions of the carton, the package insert, and black and white copy of the front panel of foil pouch The sponsor states that final printed labeling will be submitted prior to marketing. The sponsor also states that they have made all the specified labeling changes listed in the July 8, 1997 approvable letter, with the exception of the suggested pouch labeling.

Sponsor's Changes/Reviewer's Comments

APPEARS THIS WAY ON ORIGINAL

I. CARTON LABEL

1. FRONT.
   - (a) The statement of identity has been corrected to state "Ranitidine Effervescent Tablets 75 mg, Acid Reducer."
   - (b) The sponsor has replaced the letters "F.P.O." in the tablet icon with tablet symbol and the letters Z75.
   - (c) The design has been altered slightly by a decrease in the size of the pill and the addition of more bubbles.
2. SIDES.
   - (a) See I.1(a) above.
   - (b) See I.1(b) above.
   - (c) The area for the lot number and expiration date is identified
   - (d) The Tamper Resistant/Tamper Evident Statement is revised to state: "DO NOT USE IF THE INDIVIDUAL FOIL POCKET IS OPEN OR TORN."
3. BACK.
   See I.1(a) above.

APPEARS THIS WAY ON ORIGINAL

Reviewer's Comments

1. The sponsor's changes in I.1 (FRONT), I.2 (SIDES), and I.3 (BACK) above are

acceptable.

II. Package Insert.

1. FRONT.
   (a) See I.1(a) above.
   (b) See I.1(b) above.
   (c) In the section "What is Zantac 75 EFFERdose?", first bullet, the second sentence has been revised to state "One EFFERdose tablet dissolves quickly in water into a clear liquid."
   (d) The fourth bulleted statement in the section "What is Zantac 75 EFFERdose?" has been revised to state "Zantac 75 EFFERdose is an alternate choice for people who prefer a liquid medication, but enjoy the convenience of traveling with a tablet."
   (e) The statement, "This product should not be given to children under 12 years old unless directed by a doctor," has been added to the section "How should I take Zantac 75 EFFERdose?"
2. BACK
   The sponsor has revised the section titled "Clinical studies prove Zantac 75 EFFERdose is effective" to read: "Clinical studies prove Zantac 75 is effective." The header paragraph of this section has also been revised to state: "In clinical studies using Zantac 75mg Tablets (of which Zantac 75 EFFERdose is equivalent), Zantac 75 was significantly better than placebo pills in relieving heartburn."

Reviewer's Comments

1. The sponsor's changes in II.1(a), II.1(b), II.1(d), II.1(e), and 2 above are acceptable.
2. Regarding II.1(c), the sponsor should delete the word "quickly" from the sentence "One EFFERdose tablet dissolves quickly in water into a clear liquid." NOTE: The sponsor submitted samples of its product and the dissolution time does not appear to be "quickly." (See August 7, 1997-Labeling Review, Attachment 2.) The use of the word "quickly" might create a labeling problem, by implying comparison with other drugs in its class.
3. We recommend that the package insert include "Tips for Managing Heartburn."

III. Pouch:

The sponsor states that due to the small size of the pouch the following statements cannot be added to the pouch labeling: "Do not use if the individual foil pocket is open or torn," "Keep this and all drugs out of reach of children," and "Read the directions on carton, consumer leaflet, and warnings before use."

Reviewer's Comments

Because the sponsor has included in the package insert labeling (see II.1(d), above) reference to "traveling with a tablet," at some point, it should be expected that the pouch will be separated from the carton and package insert (e.g., placed in a purse,

pocket, etc.). The sponsor could remove the pill symbol from the pouch label and/or use the back of the pouch (copy not submitted) to add these warnings. Of particular concern is the "Keep out of reach . . ." and the "open or torn . . ." warnings. Currently some manufacturers of marketed OTC products are slightly increasing the size of their packages to add labeling. Apparently the sponsor is aware that the pouch is not readable, since it was blown up (200%) for this submission.

Recommendations: The sponsor submitted revised labeling as requested in the approvable letter of July 8, 1997. The following recommendations should be conveyed to the sponsor. With the exception of comment #3, the additional recommendations may be incorporated into the labeling in 6 months or at the time of the next printing, whichever comes first. The submitted final printed labeling should be identical to the revised draft labeling issued at the time of approval.

APPEARS THIS WAY
ON ORIGINAL

1. On the back panel, the first bullet under the directions states, "Dissolve 1 EFFERdose tablet completely in approximately 4-6 ounces of water." It might be more consumer friendly to state "a full glass of water." Also, a full glass (8 ounces) of water is consistent with the amount of water used in the bioequivalence studies and prototype class labeling . Therefore, we recommend that the directions to drink "4 to 6 ounces of water" be changed to drink a "full glass of water."

2. Although not a requirement at this time, it is suggested that the sponsor revise this labeling so that it is in compliance with the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. A prototype label is attached. Note that as part of the acid reducer class consumer labeling, the **"Uses"** section is revised to denote heartburn as the primary symptom, with other symptoms being secondary. The **Uses** section reads: "For relief of heartburn associated with acid indigestion and sour stomach." Under the **"Do Not Use"** section, bulleted warnings have been added to not take this product if the consumer is allergic to acid reducers and also not to take the product with other acid reducers. The latter warning is included to avoid unintentional over-medicating by consumers. The labeling information is also presented in the following specific order: **Active Ingredient(s), Purpose(s), Uses(s), Warnings, Directions, Other Information,** and **Inactive Ingredients.** No other information should precede the **"Active Ingredient"** section.

3. On the front of the package insert, the first bullet, second sentence, the word "quickly" should be removed.

APPEARS THIS WAY
ON ORIGINAL

4. Although not a requirement, it is suggested that the sponsor be asked to redesign the pouch for readability and to add the warnings (see III, above.). This could be done either by slightly increasing the size of the pouch and/or

using the back of the pouch.

5. "Tips for Managing Heartburn" should be included in the package insert.

/S/

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

/S/

APPEARS THIS WAY
ON ORIGINAL

Helen Cothran
Team Leader, HFD-560

/S/

Linda M. Katz, M. D., MPH
Deputy Director, HFD-560

Attachments

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-745
HFD-180(Folkendt)
HFD-560:Bowen/Katz/Cothran/Neuner/Robinson/Walther
HFD-560:Division File (H2 antagonists)
DOC ID:ZANTACEF.WPD

S/ 2/3/98

APPEARS THIS WAY
ON ORIGINAL

5 Page(s) Redacted

DRAFT LABELING

Attachment 2
HFD-560
Div Files

ADDENDUM TO LABELING REVIEW
Division of OTC Drug Products

AUG 7 1997

NDA #: 20-745
NAME: Zantac 75 EFFERdose (ranitidine hydrochloride) Effervescent Tablets, 75 mg. for OTC use
DATE OF SUBMISSION: April 22, 1997 CDER: April 24, 1997 DODP: May 1, 1997
DATE OF REVIEW: July 17, 1997
REVIEWERS: Rosemarie Neuner, MD, MPH, Gerald M. Rachanow, PD, JD

Background:

DODP requested samples of this product in order to see how long it takes the tablets to dissolve and how much effervescence occurs before the tablets are completely dissolved. We tested two tablets separately, dissolving each in 8 ounces (measured) of water obtained from the "cold" spigot. The first tablet dissolved in 3 minutes and 15 seconds without any agitation. The second tablet dissolved in 3 minutes 30 seconds with agitation (stirring the water with a plastic spoon). Very little effervescence (release of gas) was evident during the dissolution process.

Discussion::

1. Amount of water. The proposed labeling for this product states to dissolve 1 tablet completely in approximately 4-6 ounces (oz.) of water.

The company's labeling for its Rx Zantac EFFERdose 150 mg Tablets and Granules states to dissolve each dose in 6 to 8 oz. of water before drinking. The question was whether any change should be made in the OTC product's proposed labeling.

Recommendations:

Following discussion in the division, it was decided that it might be more consumer friendly to state a full glass of water in the directions rather than 4-6 oz.of water, but not to add time information in the labeling (deemed not necessary at this time). This change should be suggested the next time that the agency raises labeling issues.

/S/

Rosemarie Neuner, MD, MPH
Medical Officer, HFD-560

/S/

Gerald M. Rachanow, PD, JD
Regulatory Counsel, HFD-560

APPEARS THIS WAY
ON ORIGINAL

/S/

Linda M. Katz, MD, MPH
Deputy Director, HFD-560

cc: Orig. NDA
HFD-560/Div. File
HFD-180/Folkendt
HFD-560/Bowen/Katz/Neuner/Rachanow/Walther
R/D G.Rachanow 7/24/97 Addendum 8/6/97
8-7-97

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 3.

Proposed Draft H2 Drug Class Consumer Labeling

Active Ingredient (In Each Tablet) **Purpose**
H2 Antagonist XX mg .....Acid Reducer

Uses: • for relief of heartburn associated with acid indigestion and sour stomach

Warnings

Allergy Warning: Do not use if you are allergic to (the H2 antagonist) or other acid reducers.

Do Not Use: • if you have trouble swallowing
• with other acid reducers

APPEARS THIS WAY ON ORIGINAL

Stop Using This Product and See a Doctor If:
• stomach pain continues
• you need to take this product for more than 14 days

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

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.

Directions:

Adults and children 12 years of age and over:
• To **relieve** symptoms, swallow 1 tablet with a full glass of water.
• Do not take more than 2 tablets in 24 hours.

APPEARS THIS WAY ON ORIGINAL

Children under 12 years of age: Ask a doctor.

*(Note: The sponsor should add an additional bullet point under the **Directions** section advising consumers when to expect relief after taking this product based on the sponsor's clinical trial data. Sponsors can list additional direction information based on their approved NDA application.)*

Other Information: *(Manufacturers to insert in bullet format the proper temperature and storage conditions.)*

APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

Inactive Ingredients: (List in alphabetical order.)

Read Before Use: • **Warnings** • **Directions** • **Information sheet**

Keep the carton and information sheet. They contain important information.

Comments or Questions?Call toll-free 1-800-XXX-XXXX

Distributed by XXX, City, State XXXXX

APPEARS THIS WAY
ON ORIGINAL

Folkendt

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

JUN 30 1997

Application Number: NDA 20-745

Name of Drug: Nonprescription Zantac® 75 EFFERdose® (ranitidine hydrochloride) Effervescent Tablets

Sponsor: Glaxo Wellcome Inc.

Background

This application, submitted on July 2, 1996, provides for an effervescent tablet dosage form for nonprescription Zantac 75 (ranitidine hydrochloride) [Nonprescription Zantac 75 (ranitidine hydrochloride) 75 mg Tablet was originally approved in NDA 20-520 on December 19, 1995.] The drug product will be packaged in cartons of eight tablets individually sealed in strips of foil pouches. All reviews are completed and recommend approval of this application with revision to the proposed labeling.

Review

The submitted draft labeling is substantially based on the currently approved labeling for Zantac 75 (ranitidine hydrochloride) Tablets. In accordance to MaPP 6020.5, the submitted draft labeling was reviewed by the Division of Over-The-Counter Drug Products (HFD-560) on April 3, 1997. In addition to the comments and suggested revisions to the labeling cited in that review and the Medical Officer's review dated March 7, 1997, it is also recommended, because the drug product is sealed in foil pouches, that the word "BROKEN" be changed to "TORN" in the Tamper Resistant/Tamper Evident statement "DO NOT USE IF THE INDIVIDUAL FOIL POCKET IS OPEN OR BROKEN" on all labeling. In addition, if space allows, the firm should also consider adding this statement to the foil pouch label.

Conclusions

APPEARS THIS WAY
ON ORIGINAL

An approvable letter pending all requested labeling revision should be issued to the firm. Alternately, because all of the labeling revision do not appear to be substantial or controversial in nature, an approval letter based on draft labeling could be issued to this application. Because this application is for a nonprescription drug product, both the Director of the Division of Over-The-Counter Drug Products and the Acting Director of this division must concur on the action taken on this application.

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/30/97

Regulatory Health Project Manager, HFD-180

cc: Original 20-745
HFD-180/Div. Files
HFD-180/M.Folkendt, L.Talarico /S/ 6-30-97
HFD-560/S.Walther, D.Bowen, R.Neuner, L.Katz

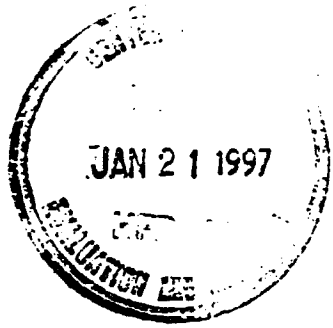
draft: MF/June 30, 1997
final: 6/30/97

CSO REVIEW

GlaxoWellcome

January 17, 1997

Stephen B. Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



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

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Fredd:

On October 17, 1996, we amended the pending New Drug Application identified above to request the Division's feedback regarding a change of the product tradename to "Zantac® 75 RapiDose." On January 15, 1997, Mr. Michael Folkendt of the Division telephoned to inform us that this tradename was not acceptable to the FDA Trademark Committee, as it implied rapid onset of heartburn relief. Mr. Folkendt requested that we withdraw this tradename and suggested that we continue to identify this product as Zantac® 75 EFFERdose® Tablets.

In compliance with this request, we are hereby withdrawing the proposed "RapiDose" tradename and request that the Trademark Committee consider the EFFERdose tradename as stated above. We would appreciate your feedback on the acceptability of this name following the February meeting of the Trademark Committee.

Please contact me at (919) 483-9884 if you have any questions concerning this submission.

Sincerely,

Thomas A. Gerding

Thomas A. Gerding
Director, Regulatory Affairs
International OTC Development

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

Telephone
919 248 2100

ITEM 13

Patent Information Pursuant to 21 U.S.C. 355 for

ZANTAC® 75 (ranitidine hydrochloride) EFFERdose®

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZANTAC® 75 EFFERdose®
Active Ingredient(s):	ranitidine hydrochloride
Strength(s):	75 mg
Dosage Form:	Tablets

Applicable Patents	Expiration Date	Type of Patent
4,128,658	July 25, 1997 • pursuant to the Uruguay Round Agreements Act, Public Law 103-465 (1994)	Drug Product Formulation / Composition Method of Use • method of treating conditions mediated through histamine H_2-receptors
4,521,431	June 4, 2002	Drug Product Formulation / Composition Method of Use • method of treating conditions mediated through histamine H_2-receptors
5,102,665	June 23, 2009 • pursuant to the Uruguay Round Agreements Act, Public Law 103-465 (1994)	Formulation / Composition

The undersigned declares that U.S. Patents 4,128,658, 4,521,431 and 5,102,665 cover the formulation, composition and/or method of use of ZANTAC® 75 (ranitidine hydrochloride) EFFERdose®. Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted,

By: _____

David J. Levy, Ph.D.
Reg. No. 27,655
Patent Counsel
Glaxo Wellcome Inc.

EXCLUSIVITY SUMMARY for NDA # 20-745

Trade Name: Zantac 75 EFFERdose Generic Name: ranitidine hydrochloride effervescent tablets

Applicant Name: Glaxo Wellcome Inc. HFD- 180

Approval Date February 26, 1998

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 questions about the submission.

a) Is it an original NDA?
YES /_X_/ NO /___/

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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.

This application/dosage form is approved based on studies submitted demonstrating bioequivalence to the currently approved tablets.

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?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6 (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.

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YES /_X_/ NO /___/

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

NDA # 20-520 Nonprescription Zantac® 75 (ranitidine hydrochloride) Tablets
NDA # 20-251 Zantac® EFFERdose® (ranitidine hydrochloride) Effervescent Tablets
NDA # 18-703 Zantac® (ranitidine hydrochloride) Tablets
NDA # 19-675 Zantac® (ranitidine hydrochloride) Syrup
NDA # 19-090 Zantac® (ranitidine hydrochloride) Injection
NDA # 19-593 Zantac® (ranitidine hydrochloride) Injection Premixed
NDA # 20-095 Zantac® GELdose® (ranitidine hydrochloride) Capsules

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 6. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 6:**

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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.

APPEARS THIS WAY
ON ORIGINAL

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 /_X_/	NO /___/
Investigation #2	YES /_X_/	NO /___/
Investigation #3	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:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

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"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

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/ 2/26/98

Signature Date

Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 2-26-98

Acting Division Director Date

cc: Original NDA 20-745 HFD-180/Division File HFD-85/Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 20-745 Supplement # ~~Circle one: SE1 SE2 SE3 SE4 SE5 SE6~~

HFD-180 Trade and generic names/dosage form: Nonprescription Zantac 75 EFFERdose (ranitidine HCl) effervescent tablets Action: AP (AE) NA

Applicant Glaxo Wellcome Therapeutic Class OTC Acid Reducer

Indication(s) previously approved B

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Indication in this application Treatment of heartburn (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

APPEARS THIS WAY ON ORIGINAL

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. **If none of the above apply, attach an explanation, as necessary.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ June 30, 1997

Signature of Preparer and Title Date

cc: Orig (NDA)/PLA/PMA # 20-745
HFD-180 /Div File
(NDA)/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

This application provides for a nonprescription drug product. The labeling is consistent with current labeling requirements and practices for nonprescription drug products (i.e., directions for use for consumers 12 years of age and older); including the statement "This product should not be given to children under 12 years old unless directed by a doctor". There have been no studies conducted or currently planned to be conducted by the firm using this drug product in the pediatric population below the age of 12.

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-745

SEP - 2 1997

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

Dear Mr. Gerding:

We acknowledge receipt on August 26, 1997 of your August 25, 1997 amendment to your new drug application (NDA) for Zantac® 75 EFFERdose® (ranitidine hydrochloride) Effervescent Tablets.

This amendment contains revised labeling for the drug product and additional copies of the Methods Validation Package submitted in response to our July 8, 1997 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is February 26, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

8/29/97

Michael Folkendt
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-745
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
HFD-560/S.Walther
DISTRICT OFFICE

Drafted by: mf/August 29, 1997
Final: 8/29/97
filename: 20745708.ACK

ACKNOWLEDGEMENT (AC)

MEMORANDUM OF TELECON

DATE: January 15, 1997

APPLICATION NUMBER: NDA 20-745; Zantac 75® RapiDose (ranitidine hydrochloride)
Non-prescription Effervescent Tablets

BETWEEN:

Name: Ms. Lorna Wilson; Assistant Director, Regulatory Affairs
Phone: (919) 483-5121
Representing: Glaxo-Wellcome Inc.

AND

Name: Michael Folkendt
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Trade name for the drug product

Background: This application, submitted on July 2, 1996, provides for a new effervescent tablet dosage form for ranitidine hydrochloride for OTC use. In a October 17, 1996 correspondence, the applicant requested comment on the proposed trade name for this drug product "Zantac 75 RapiDose". On January 7, 1997, the CDER Labeling and Nomenclature Committee found the proposed trade name, "RapiDose", unacceptable because the term "Rapid" refers to how quickly the tablet dissolves and consumers might be misled into believing that the medication goes to work more quickly, which may not be not true.

The Call: I called Ms. Wilson and informed her of the CDER Labeling and Nomenclature Committee findings and the reason why. I requested that they proposed a new trade name for this drug product, reminding her that the CDER Labeling and Nomenclature Committee meets only once a month on the fourth Tuesday. She stated that she will pass this information on and the firm will respond as soon as possible with a new proposed trade name. We then conclude the call.

/S/ 1/16/97

Michael Folkendt
Project Manager

cc: Original NDA 20-745
HFD-180/Div. File
HFD-180/CSO/Michael Folkendt
HFD-180/chemist/J.Sieczkowski

1/21/97
/S/

TELECON

MEMORANDUM OF TELECON

DATE: October 18, 1996

APPLICATION NUMBER: NDA 20-745; Zantac 75 EFFERdose (ranitidine hydrochloride) Effervescent Tablets

BETWEEN:

Name: Michael N. Joyner; Assistant Director, Regulatory Affairs
Phone: 919-483-5133
Representing: Glaxo Wellcome, Inc.

AND

Name: Michael Folkendt
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Requests for addition stability data and a revision to the Post approval stability protocol.

Background: This application provides for an effervescent dosage form for non-prescription Zantac (ranitidine hydrochloride). On October 10, 1996, the firm submitted additional stability data and analysis through the 18 month time point to support a 24-month expiry period for this product when stored between 2°C and 30°C.

The Call: At the request of the review chemist, I called Mr. Joyner and requested the following additional information:

1. The data and statistical analysis for the drug stored at 2°C.

2. Revise the post approval stability protocol to include, for the first three (3) production batches, the drug stored also under accelerated conditions.

I inform Mr. Joyner that as soon as I receive this information, I will consult the data to statistics for review. Mr. Joyner indicated that he will forward our requests to the appropriate individuals. We then concluded the call.

/S/ 10/18/96

Michael Folkendt
Project Manager

cc: Original NDA 20-745 /S/ 10/24/96
HFD-180/Div. File
HFD-180/M.Folkendt
HFD-180/J.Sieczkowski /S/ 10-25-96
HFD-180/S.Fredd

TELECON

NDA 20-745

Glaxo Wellcome, Inc.
Attention: George E. Dukes, Pharm.D.
Five Moore Drive
P.O. Box 13358
Research Triangle Park, NC 27709

JUL 18 1996

Dear Dr. Dukes:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Zantac 75 EFFERdose (ranitidine hydrochloride) Non-prescription Tablets.

You were notified in our letter dated July 15, 1996 that your application for Zantac 75 EFFERdose (ranitidine hydrochloride) Non-prescription Tablets was not accepted for filing due to non-payment of fees required under the Prescription Drug User Fee Act of 1992.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of July 16, 1996.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 14, 1996 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Michael Folkendt
Regulatory Health Project Coordinator
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-745
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
DISTRICT OFFICE

/S/ 7/17/96

APPEARS THIS WAY
ON ORIGINAL

drafted: MF/July 17, 1996/20745607.1mf
Final: 7/17/96

ACKNOWLEDGEMENT (AC)