CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 019675, S020

ADMINISTRATIVE DOCUMENTS and CORRESPONDENCE

KACUBA

Division of Gastrointestinal & Coagulation Drug Products OCT 2 2 1999

CONSUMER SAFETY OFFICER REVIEW

Applications and Materials reviewed:

Oral Formulations	NDAs	Submission Dates
Zantac (ranitidine hydrochloride) Tablets (150 & 300 mg)	18-703/SLR-057 (CBE) [2]	November 12, 1997, FPL October 6, 1999, FPL (Revised)
	18-703/SLR-058 (CBE) [1]	January 14, 1998, FPL
Zantac (ranitidine hydrochloride) Syrup (15 mg/mL)	19-675/SLR-021 (CBE) [2]	November 12, 1997, FPL October 6, 1999, FPL (Revised)
	19-675/SLR-022 (CBE) [1]	January 14, 1998, FPL
Zantac (ranitidine hydrochloride effervescent) GELdose Capsules (150 & 300 mg)	20-095/SLR-009 (CBE) [2]	November 12, 1997, FPL October 6, 1999, FPL (Revised)
	20-095/ SLR-010 (CBE) [1]	January 14, 1998, FPL
Zantac (ranitidine hydrochloride effervescent) EFFERdose Tablets and Granules (150mg)	20-251/SLR-007 (CBE) [2]	November 12, 1997, FPL October 6, 1999, FPL (Revised)
	20-251/SLR-008 (CBE) [1]	January 14, 1998, FPL

[1] Revisions to the ADVERSE REACTIONS section, "Hepatic" subsection
[2] Revisions to the PRECAUTIONS section, "Drug Interactions" subsection

Sponsor: GlaxoWellcome Inc.

Background and Summary Description:

NDA supplements 18-703/S-058, 19-675/S-022, 20-095/S-010 and 20-251/S-008, submitted under 21 CFR 314.70(c), "Special Supplement-Changes Being Effected", provide for revisions to the ADVERSE REACTIONS section, "Hepatic" subsection, of the package insert, to include reports of cholestatic hepatitis, with or without jaundice, and hepatic failure. These revisions are acceptable (See medical officer review dated March 18, 1998).

NDA supplements 18-703/S-057, 19-675/S-021, 20-095/S-009, 20-251/S-007, submitted under 21 CFR 314.70(c), provide an addition to the PRECAUTIONS section, "Drug Interactions" subsection of the package insert, regarding a ranitidine-triazolam drug-drug interaction study. The July 16, 1998 biopharmaceutics review, recommended that the firm revise the text to read:

DRAFT LABELING

[redacted]

DRAFT LABELING [redacted]

On July 20, 1998, and again on June 24, 1999, the biopharmaceutics labeling recommendation was sent to the firm by facsimile. On October 6, 1999 the firm submitted revised FPL with the requested "Drug Interactions" text. In addition, the submitted FPL included the CBE labeling revisions in the ADVERSE REACTIONS section, "Hepatic" subsection, provided for in NDA supplements 18-703/S-057, 19-675/S-021, 20-095/S-009, and 20-251/S-007.

This labeling review will evaluate both CBE changes. Since NDAs 18-703, 19-675, 20-095, and 20-251 (the four oral formulations) share the same package insert, the package insert submitted to NDA 20-095 will be cited in this review as the representative package insert.

Review

The submitted FPL, identified as "October 1999 RL-733", was compared to the labeling found acceptable in Annual Report –002, submitted May 15, 1996, to NDA 20-095, identified as "RL-205, July 1995". The following revisions were noted. Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines.

1. Throughout the labeling:

   a. The drug name [redacted] has been changed to [redacted]

   b. The word [redacted] has been changed to [redacted] and

   c. The word [redacted] has been changed to [redacted]

Comment: These are acceptable editorial revisions.

2. The product titles have been revised as follows:

DRAFT LABELING [redacted]

Comment: These revisions, requested in the November 27, 1996 approval letter for Supplement –055, are acceptable.

3. In the CLINICAL PHARMACOLOGY section, a paragraph has been added to the end of the "Clinical Trials: Gastroesophogeal Reflux Disease (GERD)" to read:

DRAFT LABELING [redacted]

4. In the INDICATIONS AND USAGE section, statement 6, Treatment of GERD" has been revised to read:

DRAFT LABELING

Comment: Revisions #3 and #4, requested in the November 27, 1996 approval letter for Supplement –005, are acceptable

5. In the PRECAUTIONS section, "Drug Interactions" subsection, a third stand-alone paragraph was added to read:

DRAFT LABELING

Comment: This revision, requested in the biopharmaceutical review dated July 16, 1998, and communicated to the firm on July 20, 1998 and June 24, 1999, is acceptable.

6. In the ADVERSE REACTIONS section, the last sentence of the first paragraph has been revised to read:

DRAFT LABELING

Comment: This is an acceptable editorial revision.

7. In the ADVERSE REACTIONS section, the "Hepatic" subsection has been revised

from:

DRAFT LABELING

to:

DRAFT LABELING

DRAFT LABELING [redacted]

Comment: This revision, submitted January 14, 1998 in Supplement –058, is acceptable (See medical officer review dated March 18, 1998).

8. At the end of the package insert, patent numbers have been added for the four formulations to read:

   a. Tablets: DRAFT LABELING [redacted]

   b. EFFERdose: DRAFT LABELING [redacted]

   c. GELdose: DRAFT LABELING [redacted]d

   d. Syrup: DRAFT LABELING [redacted]

9. The company name has been changed

   from:

   DRAFT LABELING [redacted]

   to:

   DRAFT LABELING [redacted]

10. Under the EFFERdose address, the following revision has been made to read:

    DRAFT LABELING [redacted]

11. Under the GELdose address, the following revision has been made to read:

    DRAFT LABELING [redacted]

12. The identifier has been revised

    from:

    APPEARS THIS WAY ON ORIGINAL [redacted]

    DRAFT LABELING [redacted]

to:

DRAFT LABELING

Comment: Editorial revisions identified in numbers 8 through 12 are acceptable.

Conclusions

The proposed labeling changes are acceptable and the supplements can be approved. However, for consistency between the package insert for the oral formulations and the injection formulations, the firm should be requested to revise the CLINICAL PHARMACOLOGY section, "Pharmacokinetics" subsection, the first sentence of the fifth paragraph, by changing the word "man" to "humans". This revision can be made at the next printing and reported in the next annual report.

The currently approved package insert for the oral formulations can now be considered "October 1999 RL-733".

.\S\ 10-22-99
Regulatory Health Project Manager

.\S\ 10-22-99
Division Director

cc:
NDAs 18-703/S-057 & S-058
19-675/S-021 & S-022,
20-095/S-009 & S-010
20-251/S-007 & S-008
HFD-180/Div. Files
HFD-180/A.Kacuba

APPEARS THIS WAY ON ORIGINAL

Draft: AK/August 17, 1998, October 14, 1999
R/d Initials: K.Oliver for K.Johnson/October 21, 1999
Final: AK/October 22, 1999
Filename: c:\mydocuments\ZANTAC-057-label review.doc

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 18-703/SLR-056
NDA 19-675/SLR-020
NDA 20-095/SLR-007
NDA 20-251/SLR-006

MAR 18 1997

Name of Drug: Zantac 150/300 (ranitidine hydrochloride) Tablets
Zantac (ranitidine hydrochloride) Syrup
Zantac 150/300 (ranitidine hydrochloride) GELdose Capsules
Zantac 150 (ranitidine hydrochloride) EFFERdose Tablets and Granules

Sponsor: Glaxo Wellcome Inc.

Material Reviewed

Submission Date(s): December 13, 1996

Receipt Date(s): December 16, 1996

Background and Summary Description: NDA 18-703/S-056, NDA 19-675/S-020, NDA 20-095/S-007, and NDA 20-251/S-006 were submitted in accordance with the final rule published in the Federal Register on December 13, 1994 which revised the labeling requirements for the "Pediatric Use" subsection of the labeling for prescription drugs.

Review

The submitted draft labeling was compared to the currently approved labeling (submitted on May 15, 1996 in annual report # 002 for NDA 20-295). The following differences were noted.

1. CLINICAL PHARMACOLOGY, Pharmacokinetics

The following statements were added at the end of this subsection:

DRAFT LABELING

[redacted]

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

2. PRECAUTIONS, Pediatric Use

This subsection was revised

from: DRAFT LABELING [redacted]

to: DRAFT LABELING [redacted]

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

3. DOSAGE AND ADMINISTRATION

The following subsection has been added:

DRAFT LABELING [redacted]

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

4. The tradename (Zantac) appears in all capital letters (ZANTAC) throughout the labeling.

ACCEPTABLE.

5. Listing of the Name and Place of Business of Manufacturer

A. The corporate identity has been changed appropriately from DRAFT L[redacted] DRAFT LABELING [redacted]" throughout this listing.

B. Tablets. The entire listing for the Tablets was deleted.

C. EFFERdose Tablets and Granules: The name and address of the corporation was deleted from the listing and the phrase "[redacted] was revised to "DRAFT LABELING

D. GELdose Capsules: The phrase DRAFT LABELING [redacted] was revised to DRAFT LABELING

POINTS B AND C WILL BE DISCUSSED WITH THE SPONSOR AND CHEMIST.

Conclusions

1. The proposed revisions in numbers 1, 2, and 3 above must be reviewed by the medical officer.

2. The revisions in number 5.B. amd C. above will be discussed with the sponsor and the chemist.

.\S\ [redacted] 3/18/97
Maria R. Walsh, Project Manager

3/18/97
.\S\

Walsh

NDA 18-703/S-056
NDA 19-090/S-037
NDA 19-593/S-028
NDA 19-675/S-020
NDA 20-095/S-007
NDA 20-251/S-006

JAN 24 1997

Glaxo Wellcome, Inc.
Attention: Andrew Gustafson, Ph.D.
Five Moore Drive
P.O. Box 13358
Research Triangle Park, NC 27709

Dear Dr. Gustafson:

We acknowledge receipt of your supplemental applications for the following:

NDA Number	Supplement Number	Drug Name
18-703	S-056	Zantac 150/300 (ranitidine hydrochloride) Tablets
19-090	S-037	Zantac (ranitidine hydrochloride) Injection
19-593	S-028	Zantac (ranitidine hydrochloride) Injection Premixed
19-675	S-020	Zantac (ranitidine hydrochloide) Syrup
20-095	S-007	Zantac 150/300 (ranitidine hydrochloride) GELdose Capsules
20-251	S-006	Zantac 150 (ranitidine hydrochloride) EFFERdose Tablets and Granules

Therapeutic Classifications: Standard

Date of Supplements: December 13, 1996

Date of Receipt: December 16, 1996

These supplements provide for revisions to the labeling regarding use in pediatric patients.

Unless we notify you within 60 days of our receipt 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 February 14, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning these supplemental applications should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely yours,

.\S\

Maria R. Walsh, M.S.
Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	18703	**Trade Name:**	ZANTAC (RANITIDINE HCL) TABS
Supplement Number:	56	**Generic Name:**	RANITIDINE HYDROCHLORIDE
Supplement Type:	SE8	**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
_X_ Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	
Studies Needed	No further STUDIES are needed
Study Status	

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

COMMENTS:

12-13-99 This supplement (S-056) adds info to the labeling in 16 years to 1 month of age based on clinical data. S-059, approved at the same time adds info on neonates, which was based on literature.

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

.\S\ [redacted]

Signature

12 13 99

Date

CDO/Pediatric

NDA 18-703
NDA 19-090
NDA 19-593
NDA 19-675
NDA 20-095
NDA 20-251
NDA 20-520

DEC 15 1998

GlaxoWellcome
Attention: Thomas A. Gerding
Director, Regulatory Affairs
International OTC Development
5 Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Gerding:

We acknowledge receipt of your December 1, 1998, position paper. You submitted this paper as a result of our October 28, 1998, meeting with you to discuss the August 26, 1998, Written Request for Pediatric Exclusivity Study that we issued to you for studies on Zantac.

You represent in the paper your view of the health benefit that would be obtained with the results from study RANA 20006, conducted in 4 to 11 year old children using Zantac 75 tablets. Data in 4 to 11 year old children for Zantac products have already been submitted in several supplements. Therefore, FDA would not request a study like RANA 20006 in a Written Request.

You also state in the paper that data sought in the study outlined in our August 26, 1998, Written Request are largely found in the following supplements: NDA 18-703/S056, 19-675/S020, 20-095/S007, 20-251/S006, 19-593/S028, and 19-090/S037. We agree that you have already submitted data that addresses, in part, the information that would have been generated by the study requested in the August 26, 1998, Written Request. We also acknowledge your proposal to conduct a modified study in 0-1 month old pediatric subjects. Therefore, we are amending the below listed sections of the August 26, 1998, Written Request. All other terms stated in our Written Request remain the same.

PHARMACOKINETIC/PHARMACODYNAMIC STUDY IN NEONATES

Type of study: pharmacokinetic/pharmacodynamic study in pediatric patients

Objective/rationale:

(1) To characterize the pharmacokinetics of ranitidine administered as a single intravenous dose in neonates.

(2) To characterize the pharmacokinetics of ranitidine administered as a continuous intravenous infusion, using a dosing regimen which provides therapeutically meaningful gastric acid suppression based on the data from the single dose pharmacokinetic/pharmacodynamic evaluation, in the same subjects.

(3) To collect information on the safety of single and multiple intravenous doses of ranitidine in neonates.

Indication(s) to be studied:
Any condition requiring admission to a pediatric intensive care unit where there is a need for H_2-blocker therapy.

Study design:
Open-label drug administration; single intravenous dose followed by a constant-rate intravenous infusion.

Age group in which study will be performed:
Preterm or full term neonates <1 month of age.

Number of patients to be studied:
A minimum of 12.

Entry criteria:
Inclusion criteria: Parent/legal guardian has signed written informed consent prior to study participation; male or female 0 to 1 month of age; medically established need for H_2-blocker therapy.

Exclusion criteria: Oliguria (urine flow rate <0.5 ml/kg/hr), serum creatinine ≥1.5 mg/dL, serum albumin concentration <25 g/L, overt hepatic injury (serum AST or ALT>300 IU/L), or previous administration of any H_2-antagonists or antacids.

Clinical endpoints:
Pharmacokinetic parameters to be measured: AUC, renal clearance, total body clearance, C_{max}, T_{max}, $t_{1/2}$, volume of distribution, Cp_{ss}, Cl_{ss}, and other appropriate pharmacokinetic parameters.

Pharmacodynamic parameters to be measured: Differences in gastric pH before and after ranitidine treatment for each post-dose blood sampling point, concentration-effect profiles for all patients with an initial gastric pH≤4, and any PK/PD relationships determined using acceptable modeling criteria.

Study evaluations:
Pharmacokinetic:
Single-dose study - Patients should be given the specified dose of ranitidine and have

blood samples drawn at appropriate intervals over the following 24 hours (e.g., immediately prior to dosing, 0.083, 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 12, 18, and 24 hours after dosing). [Sampling frequency and timing should take into account limitations on amount of blood draws that can reasonably be tolerated by these infants]. In addition, urine samples should be collected predose and at regular intervals post-dose for up to 24 hours.

Continuous infusion study - Following collection of the final urine sample from the single-dose study, a constant-rate intravenous infusion of ranitidine should be initiated and continued for approximately 72 hours. In addition, the rate of the infusion should be increased in predetermined increments if gastric pH falls to <4. Blood samples should be collected for serum ranitidine quantitation at a minimum of 24, 48, and 72 hours after the start of the infusion. The pharmacokinetic parameters should be calculated for each subject based on the data obtained from the blood and urine sampling. Modeling procedures, such as population pharmacokinetics and methods for using sparse sampling, may be useful in helping to minimize the amount of blood-draws needed in these young patients.

Pharmacodynamic: Gastric pH should be monitored immediately before and at specified intervals during the first 24 hours after the single-dose of ranitidine. For example, a sampling scheme that would measure gastric pH at 5-minute intervals during the first hour post-dose, at 15-minute intervals during the second hour post-dose, and once hourly thereafter for up to 24 hours is suggested. Gastric pH measurements should be obtained at prespecified times during the constant-rate infusion and should be used to titrate the ranitidine dose in order to maintain gastric pH≥4.

Safety: A baseline medical history, physical examination, and baseline clinical laboratory studies should be obtained. Physical examination and clinical laboratory assessment should be repeated at the completion of the study pharmacokinetic/pharmacodynamic assessments. Adverse event assessment should occur throughout the subject's study participation.

Drug information:

dosage form:	Ranitidine hydrochloride Injection
route of administration:	intravenous
regimen:	single dose followed by constant-rate infusion
formulation:	marketed intravenous formulation of Zantac®

Safety concerns:

Patients should be carefully monitored for adverse reactions, including clinically significant clinical laboratory abnormalities.

Statistical information:
Power of study: Power should be based on data in the literature and recommendations of experts in the field.

Pharmacokinetics: Pharmacokinetic parameters for ranitidine should be summarized using descriptive statistics and standard compartmental methods. Comparison of estimated steady-state parameters at 24, 48, and 72 hours after initiation of the continuous infusion should be made using a two-tailed, paired *t*-test.

Pharmacodynamics: Pharmacodynamic parameters should be summarized using descriptive statistics. The ranitidine concentration-effect data should be analyzed using standard pharmacodynamic effect modeling methods.

Labeling that may result from the study: Pharmacokinetic/pharmacodynamic information in neonates may be added to the Zantac prescription labeling.

Format of reports to be submitted: Full PK/PD study reports will be submitted to include the quantity and rate of ranitidine administration, ranitidine serum concentration versus time data, pharmacokinetic parameters after single dose and continuous infusion, and gastric pH recordings for each individual subject, as well as the mean data. Methods for PK/PD data and statistical analysis should also be included, in addition to any analytical assay validation criteria. Case report forms for any deaths and adverse event withdrawals should be submitted. A listing of adverse events for each individual, including clinically significant laboratory abnormalities, should be included. The study protocol, including amendments, and any publications resulting from this study should be submitted.

Timeframe for:
submitting study report: December 18, 1998

Reports of the studies that meet the terms of the Written Request dated August 26, 1998, as amended by this letter must be submitted to the Agency on or before December 18, 1998, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study should be submitted as a supplement to your approved NDA, new drug application with the proposed labeling changes you believe would be warranted

based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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

Sincerely yours,

/S/ 12/15/98

Victor Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation
and Research

cc:
Archival NDA 18-703, 19-090, 19-593, 19-675, 20-095, 20-251, 20-520
HFD-180/division files
HFD-180/A.Kacuba
HFD-180/L.Talarico
HFD-180/H.Gallo-Torres
HFD-180/K.Robie-Suh
HFD-103/V.Raczkowski
HFD-870/J.Hunt
HFD-870/C.Cronenberger
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-6/K.Roberts

Drafted by: A.Kacuba/December 15, 1998
Initialed by: B. Collier/December 15, 1998
Initialed by: V. Raczkowski/December 15, 1998
Initialed by: L.Talarico/December 15, 1998
Initialed by: K.Robie-Suh/December 15, 1998
Final: A.Kacuba/December 15, 1998
filename: c:\mydocuments\43088-ammended-WR-letter-12-15-98

REVISED PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)