CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018703, S056

Trade Name: ZANTAC TABLETS

Generic Name: RANITIDINE HYDROCHLORIDE

Sponsor: GLAXO WELLCOME RESEARCH AND DEVELOPMENT

Approval Date: 10/29/99

INDICATION(s): PEDIATRIC PATIENTS FROM 1 MONTH TO 16 YEARS OF AGE

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APPLICATION for: 018703, S056

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Approval Letter	X			
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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			
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Administrative Document(s)/ Correspondence	X			

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Application Number: 018703, S056

APPROVAL LETTER

KAN 1BA

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

OCT 29 1999

Glaxo Wellcome Research and Development
Attention: Robert Bokinski
Product Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Bokinski:

Please refer to your supplemental new drug applications dated November 13, 1996, received December 16, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zantac® (ranitidine hydrochloride) Tablets, Syrup, GELdose® Capsules, EFFERdose® Tablets and Granules, Injection, and Injection Premixed; NDAs 18-703/S-056, 19-675/S-020, 20-095/S-007, 20-251/S-006, 19-090/S-037, 19-593/S-028, respectively.

We acknowledge receipt of your submissions dated November 13, 1998 and May 13, 1999. Your submission of November 13, 1998 constituted a complete response to our December 16, 1997 action letter.

These supplemental new drug applications provide for revisions to the labeling regarding use in pediatric patients from 1 month to 16 years of age in response to 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.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted labeling (package insert submitted November 13, 1998) with the revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

1. In the package insert for the oral formulations, revise the title of Table 1 to read:

   "Table 1. Ranitidine Pharmacokinetics in Pediatric Patients Following Oral ~~IV~~ Dosing". — from above

2. In the package insert for the injection formulations, in "Table 1" in the column titled "CLp (mL/min/kg)", for the row titled "Children in intensive care (1 day – 12.6 years)", delete the value "11.7" and insert the value "10.2".

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements 18-703/S-056, 19-675/S-020, 20-095/S-007, 20-251/S-006, 19-090/S-037, and 19-593/S-028." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

Finally, we note that you have not updated the adult pharmacodynamic information as requested in the December 16, 1997 Approvable letter. In your November 13, 1998 submission, you state your rationale for not doing so includes: (1) important new information that may effect the appropriate use of Zantac is routinely added to the label through established mechanisms, (2) the request does not directly relate to the current submission, and (3) this would be a burden which will delay inclusion of the pediatric dosing information into the labeling. We refer you to our October 29, 1999 letter requesting that you submit a separate supplement under 21 CFR 314.70(b) to provide for updating the adult pharmacodynamic information when 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, contact Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/ 10-29-99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 018703, S056

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-703/S-056
NDA 19-675/S-020
NDA 20-095/S-007
NDA 20-251/S-006

DEC 16 1997

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

Dear Dr. Dukes:

Please refer to your supplemental new drug applications dated December 13, 1996, received December 16, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zantac® (ranitidine hydrochloride) Tablets, Syrup, GELdose® Capsules, and EFFERdose® Tablets and Granules, respectively.

These supplemental applications provide for revisions to the labeling regarding the use of the drug in pediatric patients. The User Fee goal date for these applications is December 16, 1997.

We have completed the review of these supplemental applications as submitted with draft labeling, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

1. Concerning the *Pharmacokinetics* subsection of the **CLINICAL PHARMACOLOGY** section of the package insert:

   a. Add a summary of the available pediatric pharmacokinetic information. This information should be presented in both text and tabular form.

   b. Add a statement regarding the potential for reduced plasma and renal clearances of ranitidine in the neonate (< 1 month old).

   c. Revise the proposed new text from:

      "There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (up to 16 years of age) and healthy adults when correction is made for body weight. The average bioavailability of ranitidine given orally to pediatric patients is 48% (±20% SD). This is comparable to that of ranitidine in the adult population."

to:

> "There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight."

Please note that the last two sentences of the proposed text should instead be included in a subsection summarizing the pharmacokinetics of ranitidine in pediatric patients.

2. Create a *Pharmacodynamics* subsection under the **CLINICAL PHARMACOLOGY** section of the package insert, and discuss the pharmacodynamics of ranitidine in pediatric subjects as compared with adults. In addition, the adult pharmacodynamic information and data should be updated.

3. Include a statement regarding the use of ranitidine in neonates to the *Pediatric Use* subsection of the **PRECAUTIONS** section of the package insert.

4. The statement of the name and place of business of the manufacturer for the oral dosage forms of Zantac® located at the end of the package insert has been revised. As a result, the statement for the name and place of business of the manufacturer for Zantac® Tablets has been deleted implying that Zantac® Tablets are manufactured by Glaxo Wellcome Inc. located at Research Triangle Park, NC. Please consider, for completeness, to include a statement of the name and place of the manufacturer for Zantac® Tablets in this section.

To facilitate review of your submissions, please provide a highlighted or marked-up copies that shows the changes that are being made to the draft labeling. If additional information relating to the safety or effectiveness of these drugs becomes available, further revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the applications.

We remind you that these changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

If you have any questions, please contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely yours,

[redacted] 12-15-97

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDAs 18-703, 19-675, 20-095, 20-251
HFD-180/Div. Files
HFD-92/DDM-DIAB
DISTRICT OFFICE
HFD-180/CSO/M.Folkendt [redacted] 12/11/97
HFD-180/H.Gallo- [redacted] 12/12/97
for HFD-870/L.Kaus
HFD-870/C.Crone [redacted] 12/12/97

Drafted by: MF/December 9, 1997
Initialed by: C.Cronenberger 12/9/97, 12/10/97
L.Talarico 12/11/97
Final: 12/11/97
filename: 18703PED.AE

APPEARS THIS WAY ON ORIGINAL

APPROVABLE (AE)