CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020745

MEDICAL REVIEW(S)

MEDICAL OFFICER LABELING REVIEW
Division of Over-The-Counter Drug Products

NDA #: 20-745
NAME: Zantac 75® EFFERdose® (ranitidine hydrochloride) Effervescent Tablets, 75 mg for OTC Use
SPONSOR: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC. 27709

APR - 3 1997

TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: February 27, 1997 **CDER:** July 2, 1996
DATE OF REVIEW: March 31, 1997
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Ms. Sakineh Walthers

Introduction:

This application was filed as a 505b(2) submission whose approval is based on the demonstration of bioequivalence to Zantac 75 Tablets (NDA 20-520). The latter formulation was approved for marketing as an over the counter drug product by the agency on December 19, 1995. This review is of draft labels and labeling (i.e., package insert, box labeling and container-closure system) for Zantac 75® EFFERdose® to be used in the treatment of heartburn, acid indigestion and sour stomach.

Description:

Zantac® 75 EFFERdose® Tablets are white to pale yellow tablets. Each tablet is engraved <<Z75>> on one face, and is identical in composition to the prescription strength Zantac® 150 mg EFFERdose™ Tablets with the exception that the 75 mg-strength tablets are half the strength of the 150 mg-strength tablets. Each tablet of Zantac® 75 EFFERdose® contains Ranitidine Hydrochloride which is equivalent to 75 mg

In addition, each tablet contains the following inactive ingredients:
Monosodium Citrate Anhydrous and Sodium Bicarbonate
Aspartame
Povidone (K30)
Sodium Benzoate

This product, which is to be dissolved in 4-6 ounces of water to give a clear solution prior to swallowing, will be packaged in tamper-proof, aluminum foil strips.

Draft Labels and Labeling:

1. Package Insert -

The package insert for Zantac® 75 EFFERdose® Tablets submitted for review by the sponsor is nearly identical in format and content to the package insert for the currently marketed formulation, Zantac 75 Tablets, with the following exceptions:

1a. Reference to the trademark name, Zantac 75 Tablets.
1b. A representative drawing of the Zantac® 75 EFFERdose® Tablet with the letters "F.P.O." stamped across drawing of the tablet. (Note: "F.P.O." stands for "For Placement Only" as per the sponsor.)
1c. Additional descriptive information about the product under bullet point 1.

1d. The addition of a fourth bullet point describing the type of individual who would be interested in using this formulation.
1e. Specific instructions under dosing and administration on how to dissolve the tablet prior to ingestion.
1f. A change in the left-sided headline for the clinical trial data.
1g. A change in the descriptive header over the clinical trial bar-graphs.

1h. The addition of a new left-sided headline for other warnings.
1i. The addition of 2 new bullet points regarding sodium and phenylalanine content.

(Note: Reviewer's comments will be restricted to items of concern, specifically changes or additions in the proposed draft labeling.)

Reviewer's Comments:

1a. The sponsor needs to correct the order of the statement of origin (SOI) located directly under the product's trademark name. In order to be in compliance with § 201.61(b), it should read as follows: "Ranitidine Effervescent Tablets 75 mg, Acid Reducer." (Note: This needs to be corrected on the present Zantac 75 mg OTC label as well.)

1b. Discussion with the sponsor's representative revealed that the letters "F.P.O." will be replaced by an icon which has not been finalized as of yet.

1d. The proposed fourth bullet point located on the front panel of the package insert which reads as follows: "Zantac 75 EFFERdose is a good choice for people who prefer a liquid medication, but don't want the inconvenience of bottled medicine away from home" is potentially misleading. Any individual who uses this medication will still have to carry the tablets around until they use them. This bullet point should, therefore, read as follows: "Zantac 75 EFFERdose is another (or alternate) choice for people who prefer a liquid medication but enjoy the convenience of traveling with a tablet" or be removed entirely.

1e. With regards to the directions on how to dissolve the tablets, the sponsor does not state whether the solution needs to be stirred in order to completely dissolve the tablet. Samples of the product have been requested from the sponsor to see if this needs to be added. In addition, it was not clear to the agency if the labeling instructions for administration of this product are in compliance with the soon to be published final OTC monograph rule regarding sodium bicarbonate containing products. These instructions will need to be modified to reflect this prior to marketing of this product.

The sponsor also needs to add the following warning line to the administration instructions for this product: "This product should not be given to children under 12 years old unless directed by a doctor."

1f. The left-sided headline at the top of the back panel of the package insert which reads as follows: "Clinical studies prove Zantac 75 EFFERdose is effective" is unsubstantiated since this application's approval is based on a bioequvalence claim and not on data from clinical efficacy trials. It also contradicts the new header over the clinical bar graphs. The headline on the back panel should be modified to state: "Clinical studies prove Zantac 75 is effective."

1g. The proposed descriptive header over the clinical trial bar-graphs should mention which dosage form (i.e., the tablet formulation) was used to generate the clinical trial data demonstrated in the graphs. This header should read as follows: "In clinical studies using Zantac 75 mg Tablets (of which Zantac EFFERdose is equivalent) Zantac 75 mg was significantly better than placebo pills in relieving heartburn."

1i. The warnings regarding sodium content and phenylalanine comply with the current CFRs. (See § 201.64 and § 201.22 respectively of the CFR.) Although it is not mandatory, the sponsor may want to add a sixth bullet point under the section "What is Zantac 75 EFFERdose?" on the front panel of the package insert informing consumers that this product contains sodium.

2. Carton Labeling:

2a. Reference to the trademark name, Zantac 75 Tablets.

2b. A representative drawing of the Zantac® 75 EFFERdose® Tablet with the letters "F.P.O." stamped across the tablet.

2c. The number of tablets or doses contained in each box has been changed to 8 tablets instead of 10 tablets for this formulation.

2d. An empty space adjacent to the sponsors name and address on one of the side flaps was noted in the proposed labeling where the lot and expiration dates are currently located on the approved box label.

2e. Reference to the trademark name, Zantac 75 Tablets.

2f. Specific instructions under dosing and administration on how to dissolve the tablet prior to ingestion.

2g. The addition of 2 new bullet points regarding sodium and phenylalanine content.

2h. Changes in the inactive ingredients in the new formulation.

Reviewer's Comments:

2a. See Reviewer's Comment 1a. above.

2b. See Reviewer's Comment 1b. above.

2d. The sponsor needs to confirm that the lot and expiration date will go in this empty space.

2f. See Reviewer's Comment 1e. above.

2g. See Reviewer's Comment 1i. Above.

2h. The changes in the inactive ingredients in the new formulation's proposed labeling are consistent with those listed in the Chemistry section of the application. The listing of the sodium content per tablet is in compliance with current OTC labeling requirements.

3. Container Label: (Note: The currently approved OTC formulation, Zantac 75 Tablets, is contained in blister dose packs. Therefore, this foil container label could not be compared.)

The sponsor provided for review a picture of only the front of the 38 mm x 33 mm double-aluminum foil, heat-sealed pouch container. The foil container has printed across it the following: the drug's name, dose strength, instructions on how to open the pouch, the manufacturer's name and address, the lot number and expiration date.

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Comments:

3. Although it is not mandatory, the sponsor may want to add a warning re: keeping the pouch out of the reach of children and keeping the pouch in the original container since the dose and administration instructions are not printed on the pouch.

APPEARS THIS WAY
ON ORIGINAL

Recommendations:

The following reviewer's comments regarding the proposed draft labeling of this product need to be addressed by the sponsor:

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Package Insert:

1. The sponsor needs to correct the order of the statement of identity (SOI) located directly under the product's trademark name. In order to be in compliance with § 201.61(b), it should read as follows: "Ranitidine Effervescent Tablets 75 mg, Acid Reducer." (Note: This needs to be corrected on the present Zantac 75 mg OTC label as well.)
2. A final draft version of the package insert with the replacement icon for the letters "F.P.O." needs to be submitted for agency review prior to the marketing of this product.
3. The proposed fourth bullet point located on the front panel of the package insert which reads as follows: "Zantac 75 EFFERdose is a good choice for people who prefer a liquid medication, but don't want the inconvenience of bottled medicine away from home" is potentially misleading. Any individual who uses this medication will still have to carry the tablets around until they use them. This bullet point should, therefore, read as

follows: "Zantac 75 EFFERdose is another (or alternate) choice for people who prefer a liquid medication but enjoy the convenience of traveling with a tablet" or be removed entirely.

4. Samples of the product have been requested from the sponsor to see if any additional information regarding dissolution of the product needs to be added to the draft labeling.

5. It was not clear to the agency if the labeling instructions for administration of this product are in compliance with the soon to be published final OTC monograph rule regarding sodium bicarbonate containing products. These instructions will need to be modified to reflect this prior to marketing of this product.

6. The sponsor also needs to add the following warning line to the administration instructions for this product: "This product should not be given to children under 12 years old unless directed by a doctor."

7. The left-sided headline at the top of the back panel of the package insert which reads as follows: "Clinical studies prove Zantac 75 EFFERdose is effective" is unsubstantiated since this application's approval is based on a bioequvalence claim and not on data from clinical efficacy trials conducted with this formulation. It also contradicts the header over the clinical bar graphs. This headline needs to be as follows: "Clinical studies prove Zantac 75 is effective."

8. The proposed descriptive header over the clinical trial bar-graphs should mention which equivalent dosage form (i.e., the tablet formulation) generated the clinical trial data demonstrated in the graphs. This header should therefore read as follows: "In clinical studies using Zantac 75 mg Tablets (of which Zantac EFFERdose is equivalent) Zantac 75 mg was significantly better than placebo pills in relieving heartburn."

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Carton Labeling:

9. See Comment #1 above re: SOI order.

10. See Comment #2 above re: replacement icon for "F.O.P.".

11. The sponsor needs to confirm that the lot number and expiration date will go into the empty space located on the flap containing the manufacturer's name and address.

12. See Comment #4 above re: dissolution directions.

13. See Comment #5 above re: sodium bicarbonate containing products.

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ON ORIGINAL

Container Label:

14. Although it is not mandatory, the sponsor may want to add warnings re: keeping the pouch out of the reach of children and that the pouch should be kept in the original box container since the dose and administration instructions are not printed on the pouch.

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15. The sponsor may want to redo this label and labeling so that it is in compliance

with the February 27, 1997 printed monograph on Proposed Labeling Requirements for OTC drug Products.

/S/

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

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ON ORIGINAL

/S/

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

cc: orig NDA
HFD-560/Div. File
HFD-180
HFD-560/MO/Neuner
HFD-560/Dep Dir/Katz
HFD-560/Div Dir/Bowen
HFD-180/PM/Folkendt
HFD-560/PM/Walther

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Labeling

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

NDA:	20-745 MAR - 7 1997
Sponsor:	GlaxoWellcome, Inc.
Drug Name:	Zantac (ranitidine hydrochloride) 75 EFFERdose Tablets for Over-the-Counter Use
Date submitted:	July 2, 1996
Date received:	July 8, 1996
Review completed:	February 28, 1997
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

In this application the sponsor seeks approval to market an effervescent formulation of Zantac 75 (ranitidine hydrochloride 75mg) over-the-counter for indications currently approved for Zantac 75®.

Background:
Zantac 75 (ranitidine hydrochloride 75mg tablet) is approved for over-the-counter marketing for treatment of heartburn, acid indigestion, and sour stomach at a dose of 75mg (1 tablet) as needed, not to exceed 2 tablets per 24 hour period (approval date, 12/19/95).

The sponsor has developed an effervescent formulation designed to provide a convenient alternative formulation for patients who may prefer a liquid dosage form instead of a tablet.

Prescription Zantac is available in 150mg and 300mg tablets, 150mg and 300mg GELdose Capsules, 150mg EFFERdose Granules, 150mg EFFERdose Tablets, and as Zantac Syrup. Prescription Zantac is approved for the following indications: short-term treatment of active duodenal ulcer; maintenance therapy for duodenal ulcer patients; treatment of pathological hypersecretory conditions (such as Zollinger-Ellison syndrome and systemic mastocytosis); short-term treatment of active, benign gastric ulcer; maintenance therapy for gastric ulcer patients; treatment of GERD symptoms; treatment of endoscopically diagnosed erosive esophagitis; and maintenance of healing of erosive esophagitis. Ranitidine doses range from 150mg daily at bedtime for maintenance therapy in duodenal ulcer and gastric patients to 150mg QID for healing of erosive esophagitis, to doses up to 6 grams per day in patients with severe pathological hypersecretory disease.

Materials Reviewed:
This submission contains no clinical efficacy data but consists of Chemistry, Manufacturing, and Controls information and bioequivalence information to support the bioequivalence of Zantac 75 EFFERdose to the commercially available Zantac 75. The submission consists of 8 volumes as follows:

- Vol. 1.1 - Index, Annotated Labeling, Overall Summary
- Vols. 1.2 through 1.5 - Chemistry, Manufacturing, and Controls
- Vols. 1.6 through 1.7 - Human Pharmacokinetics and Bioavailability
- Vol. 1.8 - Case Report Forms

Chemistry:
The sponsor states that the effervescent formulation proposed for over-the-counter marketing is of identical composition to Zantac 150mg EFFERdose Tablets but tablets are compressed to half the compression weight (750mg instead of 1500mg total tablet weight). The drug substance, ranitidine hydrochloride, is identical to and has the same source of manufacture as the currently marketed Zantac oral dosage forms. The composition of the proposed formulation is shown below:

Composition of Proposed Zantac 75 EFFERdose

Ingredient	Quantity (mg/tablet)
Ranitidine Hydrochloride Monosodium Citrate Anhydrous Sodium Bicarbonate Aspartame Povidone (K30) Sodium Benzoate	
Total Weight =	

Sodium bicarbonate, (as in the prescription drug Zantac EFFERdose) as an inactive ingredient.

In the prescription Zantac EFFERdose 150mg formulation, a single 300mg dose of the medication provides sodium bicarbonate

needed for a drug to be classified as an antacid. In a pharmacodynamic study designed to compare the effect of 300mg of the Zantac EFFERdose with that of 300mg of Zantac Tablets on gastric pH, it was found that while over a 23 hour period there was no significant difference in gastric pH or gastric acid content, there was in the first hour after dosing a significantly higher gastric pH following Zantac EFFERdose than following Zantac Tablets

This difference in gastric pH response was not felt to be clinically significant for the indications approved for ranitidine at that time, because treatment effectiveness was assessed only after several weeks of ranitidine therapy. However, it was pointed out that, should indications (such as heartburn) be approved where the efficacy is demonstrated within the first 24 hours of treatment with ranitidine, the clinical role of the pharmacodynamic effect of the sodium bicarbonate on the intragastric pH in producing the therapeutic effect may have to be evaluated.

For the current application, the sponsor has not done any pharmacodynamic study comparing the proposed Zantac 75 EFFERdose with Zantac 75 Tablets. Nevertheless, the amount of sodium bicarbonate in a single dose
represents an acid neutralizing capacity of which is well below the monograph designated value of 5mEq needed to qualify as an "antacid" drug; therefore any antacid contribution of sodium bicarbonate to the efficacy of the proposed Zantac 75 EFFERdose formulation should be negligible.

The sponsor intends that the information and data to support the approval of the proposed product be based on Zantac 75 EFFERdose to the commercially available Zantac 75 Tablets
From a clinical point-of-view this approach is acceptable for the proposed product.

Non-Clinical Pharmacology and Toxicology:
No animal pharmacology or toxicology studies are submitted. The sponsor refers to NDA 18-703 for Zantac Tablets.

Human Pharmacokinetic and Bioavailability Studies:
The sponsor has submitted the full report of one bioavailability study. This study has been reviewed by the Division of Biopharmaceutics and found to be satisfactory. Here I will briefly summarize the study and the sponsor's major findings.

I. Protocol Summary: Protocol No. RANA1001: Relative Bioavailability of the 75mg Ranitidine Effervescent and Swallow Tablets in Healthy Adult Male Subjects. (NDA Vol. 1.6, p. 48 through Vol. 1.7, p. 233).

This was a randomized, open-label, 2-way crossover study to be done in 36 healthy male subjects. The primary objective of this study was to determine the bioavailability of orally administered the 75mg ranitidine effervescent tablet relative to the 75mg ranitidine swallow tablet. Screening procedures included taking of a medical history, physical examination, and clinical laboratory studies. Informed consent was obtained. Subjects were to be healthy males aged 18-50 years, weighing between 135 and 200lbs and within 15% of their ideal body weight. Criteria for exclusion were: acute illness within 30 days prior to study; clinically significant medical condition; conditions that might interfere with drug metabolism and/or disposition; previous gastrointestinal surgery, other than appendectomy, performed more than 3 months prior to study; history of abnormal bleeding tendencies or thrombophlebitis; history of hepatitis B or HIV infection; ethanol abuse; drug abuse; smoking >20 cigarettes or 2 cigars daily or difficulty abstaining from tobacco use from 4 hours prior to till 4 hours after drug administration; chronic use of any over-the-counter medication; use of any prescription medication within 7 days prior to study or during study; difficulty abstaining from use of caffeine or other xanthines for 24 hour prior to till 16 hours after dosing; history of psychiatric illness; hypersensitivity to any H_2 - receptor antagonist; participation in an investigational study within 30 days prior to study treatment. Subjects were randomized to treatment sequence and received treatments as inpatients at a clinical research center. For the effervescent formulation the tablet was dissolved (5 minutes) in 120ml of water and the resulting solution was swallowed. The glass was then rinsed with an additional 120ml of water and this water was consumed also. The swallow tablet was taken with 240ml of water. Subjects were to fast at least 8 hours prior to drug dosing. Study treatments were begun within 14 days of screening and there was a wash-out period of 3 to 7 days between treatments. The sponsor's flow chart of study procedures is shown below:

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Study RANA1001: Flow Chart/Time and Events Table

	Screening Phase[a]	Dosing Period 1	Washout 72 hrs to 7 days	Dosing Period 2	Post-Study[b] Phase
Informed Consent	X				
Medical History	X				
Physical Examination	X				X
Vital Signs[c]	X	X		X	
Blood Chemistry and Hematology	X				X
Urine Drug Screen	X				
HIV and Hepatitis B Screen	X				
Admission to Unit		X		X	
Drug Administration		X		X	
Adverse Event Monitoring		X	X	X	X
Blood Sampling[d]		X		X	
Discharge from Unit		X		X	X

[a] Must occur within 14 days prior to dosing Period 1.
[b] 16 hours after administration of the final study dose and prior to discharge from the unit.
[c] Oral temperature, blood pressure, heart rate, and respiratory rate.
[d] Prior to dosing (baseline), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, and 16 hours after dosing.

sponsor's table, NDA Vol. 1.6, p. 134

Clinical laboratory tests included hemoglobin, hematocrit, WBC count with differential, platelet count, albumin, ALT (SGPT), AST (SGOT), BUN, creatinine, calcium, chloride, glucose, inorganic phosphorus LDH, potassium, sodium, total bilirubin, bicarbonate, total protein, alkaline phosphatase, HIV antibody, hepatitis B surface antigen, drug screen. Adverse events were recorded along with severity, seriousness, and course.

Study medications used were ranitidine 75mg effervescent tablets, batch number GFD 30007, expiration date 3/31/96 and ranitidine 75mg swallow tablets, batch number A94B58, expiration date 2/29/96.

Primary analysis of Cmax, AUC_{∞}, λ_z, and $t_{½}$ were done after log-transformation of the data. C_{max} and AUC were compared between treatments using a 90% confidence interval derived from two one-sided t-tests; t_{max} was analyzed using Koch's method, a nonparametric method for 2 x 2 crossover designs. The sponsor indicates that the sample size of 36 subjects should be adequate to detect a 20% difference in either AUC or C_{max} between treatments with greater than 80% power.

II. Results: *Enrollment, Demographics, and Disposition of Subjects:* Thirty-seven subjects were entered into this study. One subject (#3971) completed only the first

treatment period because of developing strep throat and a urinary tract infection requiring medication (penicillin). All 36 other subjects completed the study. Mean age was 26.3 years , 27 subjects were White, 5 were Black, 4 were Hispanic, and 1 was Oriental. Twenty-two percent (8 subjects) reported some use of tobacco.

Pharmacokinetics: Pharmacokinetic parameters for the two treatments are summarized in the following table. Data from subject #3971 is included in the summary pharmacokinetic calculations for treatment rantidine 75mg swallow tablet but not in the treatment comparisons.

RANA1001: Pharmacokinetic Comparison of Zantac EFFERdose 75mg Tablets with Zantac 75mg Film-Coated Tablets

Parameter		Zantac EFFERdose 75mg Tablet (A) (n=36)	Zantac 75mg Film-coated Tablet (B) (n=37)	Ratio A/B (n=36)		
				mean	90%CI	p-value
AUC_{last} (ng*hr/mL)	Mean %CV 95%CI	1194.53 22.19 1138.65-1253.16	1188.71 22.49 1133.09-1247.00	1.00	0.95-1.06	0.884
AUC_{∞} (ng*hr/mL)	Mean %CV 95%CI	1246.70 22.84 1189.42-1306.74	1256.85 22.17 1199.10-1317.38	0.99	0.94-1.05	0.806
C_{max} (ng/mL)	Mean %CV 95%CI	225.09 26.80 209.89-241.39	213.46 24.33 199.05-228.92	1.05	0.97-1.14	0.283
t_{max}[1] (min)	Mean %CV 95%CI	2.000 55.059 0.667-6.000	2.500 42.019 0.667-6.000	A-B: -0.417	-1.000-0.000	0.042
λ (1/hr)	Mean %CV 95%CI	0.2503 13.7883 0.2381-0.2630	0.2504 18.3190 0.2383-0.2632	1.00	0.94-1.06	0.009
Half-life (hr)	Mean %CV 95%CI	2.77 15.697 2.636-2.911	2.768 19.127 2.634-2.909	1.00	0.94-1.06	0.009

[1] Values reported for t_{max} (min) are the median and ranges for Treatment arms A, B, and the Ratio A/B.
CV = Coefficient of Variation (Standard Deviation/Mean*100)
Mean Values are Geometric Least-Square Mean

sponsor's table, modified, NDA Vol. 1.1, p. 34

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ON ORIGINAL

Criteria for bioequivalence were that the 90% confidence intervals (CI) around the mean treatment ratios for AUC_{last}, AUC_{∞} and C_{max} were within the range of
The sponsor concluded that the ranitidine effervescent tablet formulation is

bioequivalent to the 75mg ranitidine swallow tablet. However, with regard to individual values, in some instances for some patients the ratio of A/B was outside the acceptable range; for example, for AUC_{last} the ratio was slightly low for 3 subjects (0.66, 0.77, and 0.79) and slightly high for 5 subjects (1.31, 1.34, 1.37, 1.53, and 1.53).

Safety: Only one subject reported any adverse event. This was subject #3971, a 30 year old smoker with unremarkable physical exam, medical history and baseline laboratory values, who developed strep throat and a urinary tract infection four days after completing study period 1 (ranitidine 75mg swallow tablet) requiring antibiotic treatment. Both events were judged mild and unrelated to study drug. There were no serious adverse events or deaths in this study. There were no clinically important changes in physical examination (other than possible worsening of untreated tinea versicolor present at baseline in one patient) or vital signs over the course of the study.

With regard to laboratory studies, two subjects (#3967 and #4000) had an unexplained drop in hematocrit during the study (45.3 to 39.0 and 42.6 to 37.0, respectively) and two subjects (#3993 and #3988) had significant increases in serum glucose (96 to 151mg/dl and 87 to 145mg/dl, respectively).

III. Reviewer's Comments: By the sponsor's analyses the ranitidine 75mg effervescent formulation and the ranitidine 75mg swallow tablet formulation were bioequivalent. FDA Biopharmaceutics agrees that bioequivalence has been demonstrated. (See Biopharmaceutics Review by R. Pradhan dated 1/27/97). Both formulations were well-tolerated in this study.

Clinical Efficacy and Safety Data:

No clinical efficacy information is included in this submission. The sponsor Refers to NDA 18-703 for Zantac Tablets, and to NDA 20-520 for Zantac 75 Tablets for over-the-counter use. Zantac 75mg Tablets for over-the-counter use has been shown to be effective for relief of heartburn, acid indigestion and sour stomach. According to the sponsor's analyses the Zantac EFFERdose formulation is bioequivalent to the Zantac 75 Tablet formulation.

No effervescent low-dose (< 150mg) formulation of Zantac is marketed anywhere in the world. However, 150mg and 300mg effervescent formulations are approved in the U.S. and Denmark. Zantac 75 Tablet for over-the-counter use was first approved for marketing on 12/30/94 in the United Kingdom and has been marked in the U.S. since 12/95; it is marketed also in Holland, Mexico and Australia.

Most of the safety information to support this application comes with the long marketing experience available with prescription Zantac and from the safety database for over-the-counter Zantac 75. The current submission does not suggest any new problems with the proposed effervescent formulation.

Benefit/Risk Assessment:
Zantac EFFERdose 75mg tablets represents a meaningful benefit to the consumer by providing an alternate dosage form for patients who prefer a liquid formulation while maintaining the convenience and stability of a solid formulation. The long history of safe use of ranitidine at prescription doses and the available information on use of non-prescription Zantac 75 support a good safety profile for the proposed Zantac EFFERdose 75mg product.

The benefit-risk assessment is favorable for the approval of the proposed product.

Labeling:
The sponsor's proposed labeling for Zantac EFFERdose 75mg Tablets, is attached to this review as Appendix F. Regarding the proposed labeling, I have the following comments and recommendations.

Package Insert:

1. In the first bullet point under "What is Zantac 75 EFFERdose?" change the sentence: "One EFFERdose tablet dissolves quickly in water into a clear, easy-to-swallow liquid without the grit and gas of other effervescent heartburn remedies" to read: "One EFFERdose tablet dissolves in water into a clear liquid."

   The deleted information seems unduly promotional. The word "quickly" is not defined or qualified; "easy-to-swallow" may be more dependent on the patient than on the particular liquid formulation; and no information is given to substantiate less grit and gas than other remedies.

2. The topic "Clinical studies prove Zantac 75 EFFERdose is effective" may imply that clinical efficacy studies were done with Zantac 75 EFFERdose. However, the heading for the bar graph adds some clarity.

3. Dividing the section "When should I see a doctor?" into two sections ("When should I see a doctor" and "What other things should I be concerned about?" seems to me to be a good idea (as opposed to adding more bullet points to the existing one section) and the information is reasonably distributed.

Conclusions and Recommendations:
I recommend approval of Zantac EFFERdose 75mg Tablets for treatment of heartburn, acid indigestion and sour stomach on the basis of its demonstrated bioequivalence to Zantac 75 Tablets and pending satisfactory chemistry review.

The proposed labeling for the product should be revised as suggested in the first comment under **"Labeling"** above.

These comments and recommendations may be conveyed to the sponsor.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 3/7/97

cc:
NDA 20-745
HFD-180
HFD-180/SFredd
HFD-180/KRobie-Suh
HFD-181/MFolkendt
HFD-180/JChoudary
HFD-180/EDuffy
HFD-710/Biometrics
HFD-426/Biopharmaceutics
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