CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020745

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 27 1997 DO/Kendt

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-745 Submission Date: 07-02-96

Zantac® 75 EFFERdose® Tablet for OTC Use

Ranitidine Effervacent Tablet 75 mg

Sponsor: Glaxo Wellcome Inc., Five Moore Dr., P.O. Box 13398
Research Triangle Park, NC 27709

Priority: 1S

Type of Submission: New Formulation Reviewer: Rajendra S. Pradhan, Ph.D.

Synopsis:

Ranitidine (RN) is currently marketed in the U.S. as 150 and 300 mg oral tablet, syrup, 150 and 300 mg GELdose™ Capsules, 150 mg EFFERdose™ Tablets and 150 mg EFFERdose™ Granules as prescription products. RN is also marketed as 75 mg tablet over-the-counter (OTC). The subject of this NDA submission is Zantac 75 EFFERdose, a new proposed dosage form of RN for OTC use in the treatment of episodic heartburn.

The sponsor has conducted a satisfactory study to show bioequivalence (BE) between 75 mg swallow tablet (reference) and 75 mg effervescent tablet (test). The sponsor is requesting an approval of this new dosage form based solely on this BE study. In other words, the sponsor has not performed any clinical safety-efficacy trial for this new dosage form.

Recommendation:

The 75 mg ranitidine effervescent tablet (test) and 75 mg ranitidine swallow tablet (reference) are bioequivalent according to the The proposed dissolution specification is satisfactory. This submission is acceptable to the Div. of Pharmaceutical Evaluation II (DPE-II), OCPB.

/S/ 1-22-97

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

/S/

FT initialed by Lydia Kaus, Ph.D 01/23/97

cc: NDA 20-745, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Lesko), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-205 (FOI), Drug File (Clearance Bott)

Background:
This new drug application is submitted to obtain over-the-counter marketing approval of an oral, effervescent dosage formulation of the currently approved Zantac® 75 tablet. The information and data contained in this application to support the approval of Zantac® 75 mg EFFERdose™ tablet is based on the dosage formulation in comparison to the approved Zantac® 75 swallow tablet. As this application is for a new formulation of a drug and route of administration already approved, no clinical efficacy studies in patients have been conducted.

Formulation:
The drug substance, ranitidine hydrochloride, is identical to and has the same source of manufacture as the currently marketed Zantac® 75 swallow tablet. The Zantac® 75 mg EFFERdose™ tablet

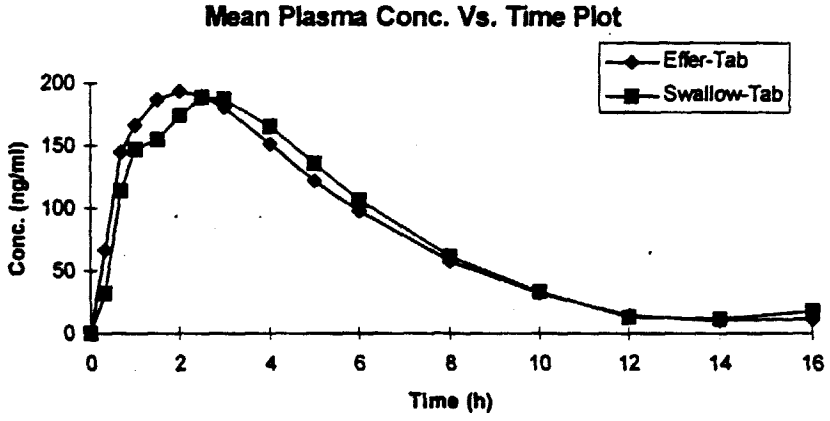
Zantac® 75 mg EFFERdose™ are white to pale yellow, round, engraved <<Z75>> on one face, tablets containing 75 mg of ranitidine (as hydrochloride).

The following table lists the composition of the dosage form:

Ingredients[1]	Quantity (mg/tablet)
Ranitidine Hydrochloride Monosodium Citrate Anhydrous Sodium Bicarbonate Aspartame Povidone (K30) Sodium Benzoate	
Total Weight =	

Bioavailability of Zantac® 75 mg EFFERdose™ Tablet:
The relative bioavailability of the 75 mg RN effervescent tablet relative to the 75 mg RN swallow tablet was determined in 36 healthy male subjects in an open-label, randomized, two-way crossover study. The subjects received one of two treatments: one 75 mg RN [1] tablet (Zantac® 75, swallow tablet) or 75 mg effervescent tablet (proposed Zantac® 75 mg EFFERdose™) All doses were administered orally after a minimum of an 8 hour fast, and serum samples were collected periodically during a 16 hour period following dosing.

The following figure summarizes the mean plasma concentration versus time profile for the two treatments.



[1] NDA20-251/Amendment (AC) Review by Patrick J Marroum, OCPB, 8-31-93

The following table summarizes the pharmacokinetic parameters and the bioequivalence analysis. Criteria for establishing bioequivalence of ranitidine 75 mg effervescent and swallow tablet formulations is that the 90% confidence intervals for the ratios of AUC_{last}, $AUC_{0-\infty}$ and Cmax for both treatments (using log-transformed data) are within . The study result show that the bioequivalence criteria was met satisfactorily.

	Treatment A ranitidine 75 mg effervescent	Ratio A/B	Treatment B ranitidine 75 mg swallow
AUC_{last} (ng.h/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	 1194.53 (1138.65 - 1253.16)	 1.00 (0.95 - 1.06)	 1188.71 (1133.09 - 1247.05)
$AUC_{0-\infty}$ (ng.h/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	 1246.70 (1189.42 - 1306.74)	 0.99 (0.94 - 1.05)	 1256.85 (1199.10 - 1317.38)
Cmax (ng/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	 225.09 (209.89 - 241.39)	 1.05 (0.97 - 1.14)	 213.46 (199.05 - 228.92)
tmax (hr) Median Range 95% CI Median Difference 90% CI	 2.00 (0.67 - 6.00) (1.50 - 2.50)	 A - B = -0.42 (-1.00 to 0.00)	 2.50 (0.67 - 6.00) (2.50 - 3.00)

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Appendix I

Relative Bioavailability of the 75 mg Ranitidine Effervescent and Swallow Tablets in Healthy Adult Male Subjects

Study #: RANA1001

Objectives:
To determine the bioavailability of the 75 mg ranitidine effervescent tablet relative to the 75 mg ranitidine swallow tablet when taken orally by healthy adult male subjects.

Study Design:
This was a single-center, randomized , open-label, two-way, cross-over study in 36 healthy adult male subjects. The study lasted approximately 40 days. Thirty-seven (37) adult healthy male subjects between the ages were enrolled in this study and 36 subjects completed the study. All doses were administered orally after a minimum of an 8 hour fast. Study treatment was started within 14 days of an initial screening visit. Subjects were admitted to the study unit the evening before dosing and remained in the unit for at least 16 hours after dosing. There was a minimum of 72 hours and a maximum of 7 days between each treatment.

The two treatments were:
Treatment A: 75 mg RN effervescent tablet (test); and
Treatment B: 75 mg RN swallow tablet (reference)

Formulation: Zantac® 75 mg EFFERdose™ batch # = GFD30007, size = 800,000

Withdrawals: Data from all thirty-six subjects who completed both periods of the study were included in the pharmacokinetic and statistical analysis. Subject 3971 completed only the first period of the study (swallow tablet). He was withdrawn due to two adverse events which were unrelated to study drug, viz. Strep throat and urinary tract infection.

Results:
The criteria for establishing bioequivalence of RN 75 mg effervescent and swallow tablet formulations was that the 90% confidence intervals for the ratios of AUC_{last}, $AUC_{0-\infty}$ and Cmax for both treatments are within the range The analysis using the log-transformed data met this criteria.

	Treatment A ranitidine 75 mg effervescent	Ratio A/B	Treatment B ranitidine 75 mg swallow
AUC_{last} (ng.h/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	1194.53 (1138.65 - 1253.16)	1.00 (0.95 - 1.06)	1188.71 (1133.09 - 1247.05)
$AUC_{0-\infty}$ (ng.h/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	1246.70 (1189.42 - 1306.74)	0.99 (0.94 - 1.05)	1256.85 (1199.10 - 1317.38)
Cmax (ng/ml) Geo. LS Mean 95% CI Mean Ratio 90%CI	225.09 (209.89 - 241.39)	1.05 (0.97 - 1.14)	213.46 (199.05 - 228.92)
tmax (hr) Median Range 95% CI Median Difference 90% CI	2.00 (0.67 - 6.00) (1.50 - 2.50)	A - B = -0.42 (-1.00 to 0.00)	2.50 (0.67 - 6.00) (2.50 - 3.00)

Conclusion:

The 75 mg ranitidine effervescent tablet (test) and 75 mg ranitidine swallow tablet (reference) are bioequivalent according to the two one-sided tests procedure and 90% confidence interval range using log-transformed data.

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