CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020605

Trade Name : ZOFRAN SOLUTION 4MG/5ML

Generic Name: Ondansetron

Sponsor : GalaxoWellcome

Approval Date: January 24, 1997

NDA 20-605
Zofran (ondansetron) Solution
Glaxo Wellcome Inc.

Volume 1 of 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-605

GlaxoWellcome Inc.
Attention: George Dukes, PharmD
Five Moore Drive
P.O. Box 13358
Research Triangle Park, NC 27709

JAN 24 1997

Dear Dr. Dukes:

Please refer to your new drug application dated June 22, 1995, received June 23, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron HCl) Solution, 4 mg/5 ml.

We acknowledge receipt of your submissions dated July 25, August 28, and December 19, 1996. The User Fee goal date for this application is January 27, 1997.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on August 28, 1996. Accordingly, the application is approved effective on the date of this letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Sufficient stability data has been submitted to support an 18 month expiration date.

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, please contact Kati Johnson, Consumer Safety Officer, at (301) 443-0487.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-605

Glaxo Wellcome Inc.
Attention: John West
Five Moore Drive
Research Triangle Park, NC 27709

MAY 31 1996

Dear Mr. West:

Please refer to your June 22, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron hydrochloride) Solution.

We acknowledge receipt of your amendments dated August 24 and October 10, 1995 and January 18, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit an adequate response to our letter dated May 23, 1996 requesting additional chemistry information.

In addition, please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. The labeling should be identical in content to the draft labeling submitted on June 22, 1995.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, 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 application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

KJ 5/23/96
SBF 5/31/96

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-180/K.Johnson
HFD-103/P.Botstein
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: kj/May 22, 1996/c:\wpfiles\cso\n\20605605.2kj

APPROVABLE (AE)

18 Page(s) Redacted

1774/0
Submission

NDA 20-605

PATENT INFORMATION

Amendment to Patent Information For ZOFRAN® (ondansetron hydrochloride) Oral Solution

Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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

Trade Name:	**ZOFRAN® Oral Solution**
Active Ingredient:	Ondansetron Hydrochloride
Patent Number:	5,578,628
Expiration Date:	June 24, 2006 (GATT Extended - a Certificate of Correction has been filed with the USPTO to correct the expiration date listed on the face of this patent)
Type of Patent:	Method of Use in treating nausea and vomiting
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 5,578,628 covers the method of use of ondansetron hydrochloride in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: December 18, 1996

By: Robt T. Hrubiec

Robert T. Hrubiec, Ph.D.
Patent Agent
Glaxo Wellcome Inc.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-605 Trade (generic) names Zofran (ondansetron) Solution

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

This is a new formulation which is bioequivalent to the tablet formulation and which contains dosing information for pediatric patients

Kate Johnson
Signature of Preparer

1/22/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Glaxo Inc. Research Institute

June 22, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ORIGINAL

Re: NDA 20-605; Zofran® (ondansetron hydrochloride) Oral Solution
Original Application

NDA 20-103; Zofran® (ondansetron hydrochloride) Tablets
General Correspondence

Dear Sir/Madam:

Pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act, we are submitting a New Drug Application for Zofran® (ondansetron hydrochloride) Oral Solution, 4mg/5mL.

This New Drug Application provides chemistry, manufacturing, and controls data to support this dosage form as an oral dosing alternative to Zofran Tablets, 4mg and 8mg, in the chemotherapy and postoperative settings. Data from one clinical study investigating the relative bioavailability of Zofran Oral Solution and Zofran Tablets, 4mg, is also provided.

This document contains a statistical analysis of 12 months stability data from three commercial-scale batches manufactured at the proposed site for commercial manufacture. A copy of this analysis is provided on diskette in Volume 1 of the application. The data presented support an expiry of greater than 24 months when the product is stored upright between 15° and 30°C and protected from light. Each batch was sourced from three different production batches of ondansetron hydrochloride dihydrate drug substance which is identical to and has the same source of manufacture as that used for the currently marketed presentations of Zofran Injection and Zofran Tablet. Draft labeling incorporating changes to the current package insert for Zofran Tablet relevant to the new presentation is presented in Volume 1. Methods validation is presented in Volume 2. Three additional copies of this volume (bound in red) are included in the submission. A copy of the letter documenting payment of the initial application fee is attached.

Glaxo certifies that it did not and will not use in any capacity the service of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Field copies of this application have been sent to:

Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA 30309
Attn: Robert Coleman

and

Food and Drug Administration
International Programs Branch
Division of Field Investigations
HFC-134, Room 1223
5600 Fishers Lane
Rockville, MD 20857
Attn: Nancy Haggard

If you have any questions regarding this New Drug Application, please contact me at (919) 990-6059.

Sincerely,

John West

John B. West,
Senior Regulatory Affairs Associate
Regulatory Affairs

MAY 3 1996

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-605, amendment BB Submission Date: 01-18-96
Zofran®
Ondansetron HCl Oral Solution, 4 mg/5 ml
Sponsor: Glaxo Wellcome Inc., Research Trangle Park, NC
Reviewer: Rajendra S. Pradhan, Ph.D.
Type of Submission: Sponsor's response to request from OCPB/DPEII

Background: The sponsor has submitted additional information regarding bioequivalence study "A study to investigate the relative bioavailability of Ondansetron Syrup and Zofran Tablets 4 mg" at the request of OCPB reviewer (Philip Colangelo, Pharm. D., Ph.D.). The request was conveyed to the sponsor through the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and appeared in the OCPB/DPEII review of NDA 20-605 as follows:

Comments to be sent to the Sponsor:

2. The Assay Validation Report for Study was missing . It is recommended that the sponsor provide this report, which should include the results of extraction efficiency experiments for the quality control samples. These later results would provide additional evidence for the acceptance of the plasma ondansetron concentration data for Subjects #7 and #8.

Sponsor's Response:

was used to carry out the assay of Ondansetron in human plasma samples.
Limit of Quantitation: 1 ng/ml. However, occasionally the precision of the assay at the 1 ng/ml level was unacceptable and for this reason a higher level of 3 ng/ml was chosen.
Specificity:

Recommendation:

The Division of Pharmaceutical Evaluation II has reviewed the information provided by the

sponsor on the assay validation of plasma ondansetron concentration estimation and found this information to be acceptable. No further information is needed.

5-2-96

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

FT initialed by Lydia Kaus, Ph. D. LCK 5/3/96

cc: NDA 20-605, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-860 (Malinowski), HFD-880 (Fleischer), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-205 (FOI), HFD-850 (Lesko)

Johnson OCT 25 1995

NOV 2 1995

NDA: 20-605 **Submission Date:** June 22, 1995

Zofran® (Ondansetron Hydrochloride Dihydrate) Oral Solution, 4mg/5ml
(±)-1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride dihydrate

Sponsor: Glaxo Wellcome Inc.
Research Triangle Park, NC

Type of Submission: Bioequivalence study to support approval of an oral solution dosage form

OCPB Reviewer: Philip Colangelo, Pharm.D., Ph.D.

Synopsis:

The sponsor has submitted this NDA to support the approval of Zofran® Oral Solution 4mg/5ml as an alternative oral dosage form to the currently marketed 4mg and 8mg Zofran® tablets for the prevention of nausea and vomiting associated with cancer chemotherapy, radiation therapy, and surgery involving general anesthesia. In the proposed labeling for the oral solution (see **Appendix 2**), the sponsor states that 5ml of the solution is bioequivalent to one 4mg Zofran® tablet and that the solution and tablet may be used interchangeably. Based on this, the labeling also states that 10ml of the solution is bioequivalent to one 8mg tablet or two 4mg tablets. In order to substantiate the claim of interchangeability between these two dosage forms, one primary study was submitted to evaluate the bioequivalence of 5ml (4mg) of the solution and the 4mg tablet (Study The results of this study, which was the focus of this review, are summarized as follows:

Study "A Study to Investigate the Relative Bioavailability of Ondansetron Syrup and Zofran Tablets 4mg"

This was a randomized, open-label, two-way crossover study to evaluate the bioequivalence of ondansetron 4mg/5ml oral solution to that of the market image 4mg tablet in 16 healthy male subjects. Each subject received a single 4mg dose of the tablet or the oral solution on two separate occasions with a 7 day interval between the dosing occasions. The 90% confidence intervals, using the 2 one-sided test, for log-transformed AUCinf and Cmax ratios were (91%,120%) and (82%,109%), respectively. No statistical differences were detected in the respective median and mean values for Tmax and T½. There were no serious adverse events reported in this trial. The results indicated that the 4mg/5ml oral solution dose was bioequivalent to the 4mg tablet dose in the 16 healthy adult males studied.

The sponsor also resubmitted two studies that were previously filed under the approved Zofran® tablet NDA 20-103 and were previously reviewed by the Division of Biopharmaceutics. This was in response to the Agency's request to support the labeling statement that 10ml (8mg) of the solution is bioequivalent to one 8mg tablet or two 4mg tablets. No further review of these studies is needed and a copy of the previous Biopharmaceutics review of each study is provided in **Appendix 1** for reference. The following is a summary of the results from these studies, as they relate to this submission:

Study _____ **"An Evaluation of the Pharmacokinetics of Ondansetron in Healthy Male Volunteers After 8mg Oral Doses, One Tablet, and One Solution"**

This crossover study compared the relative bioavailability of ondansetron given as the 8mg tablet and as an 8mg oral solution, using the 2mg/ml injection formulation, in 24 healthy male subjects. It was concluded by the Biopharmaceutics reviewer that the 90% confidence intervals for AUCinf (92%,107%), Cmax (89%,101%), and Tmax (91%,119%) demonstrated that the 8mg tablet and the 8mg injection solution, when taken orally, were bioequivalent.

Study _____ **"An Evaluation of the Steady-State Pharmacokinetics of Ondansetron After 1, 4, and 8mg Oral Doses"**

This crossover study evaluated the dose proportionality of ondansetron after single and steady-state oral tablet doses of 1, 4, and 8mg (administered every 8 hours for 7 doses) in 25 healthy male subjects. Since the drug is marketed as the 4 and 8mg tablets, the most relevant comparison was between the 4 and 8mg doses. After steady-state dosing, no statistically significant difference was detected in the mean dose-normalized AUC(0-8) values between these two doses ($p > 0.05$). Simple linear regression analysis of AUC(0-8) at steady-state *vs.* dose produced a correlation coefficient (r) of 0.9999. A significant difference was detected in the mean dose-normalized Cmax between the 4 and 8mg doses under both conditions (i.e., ~11% increase at 8mg *vs.* 4mg; $p < 0.05$) and in the mean dose-normalized AUCinf after single dose administration (i.e., ~12% increase at 8mg *vs.* 4mg; $p < 0.05$). The mean estimates of the terminal rate constants were not statistically different between 4 and 8mg after either single and steady-state doses ($p > 0.05$). The conclusion of the Biopharmaceutics reviewer was that there was dose proprotionality between the 4 and 8mg doses under steady-state conditions.

In conclusion, the results from these studies indicated (1) there was bioequivalence between the 4mg/5ml oral Zofran® solution and the 4mg market image Zofran® tablet, (2) there was bioequivalence between the 8mg tablet and 8mg of an injectable solution when taken orally, and (3) there was dose proportionality between the 4 and 8mg tablet doses under steady-state conditions. Also, the 4mg and 8mg tablets are

compositionally proportional (see **Appendix 2**). Based on these findings, the labeling claim that 10ml (8mg) of the oral Zofran® solution is bioequivalent to the 8mg tablet or two 4mg tablets appears to be substantiated.

Comments To Be Sent To Sponsor:

1 The contribution of the extrapolated AUC to the total AUCinf was >20% for several subjects in Study Therefore, it is recommended that the sponsor perform a re-assessment of bioequivalence of the 4mg/5ml solution and the 4mg tablet using the AUC from time zero to the last quantifiable plasma ondansetron concentration, i.e., AUC(0-LQC), in addition to that already performed using AUCinf.

2. The Assay Validation Report for Study was missing. It is recommended that the sponsor provide this report, which should include the results of extraction efficiency experiments for the quality control samples. These latter results would provide additional evidence for the acceptance of the plasma ondansetron concentration data for Subjects #7 and #8.

General Comments:

3. In future bioequivalence studies, it is recommended that the sponsor compare the equivalence of two formulations using the *highest* strength (or dose) at which dose proportionality has been shown and the dosage strengths are compositionally proportional. In this way, extrapolation of the bioequivalence to a lower strength (or dose) will have greater justification.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed Study of NDA 20-605 and has found it to be acceptable provided that Comments 1 and 2 have been adequately addressed by the sponsor. Comment 3 may be conveyed to the sponsor as deemed appropriate.

Philip M. Colangelo 10/12/95
Philip Colangelo, Pharm.D., Ph.D.
Pharmacokinetics Evaluation Branch II

RD Initialed by Lydia Kaus, Ph.D. LCK 10/19/95

FT Initialed by Mei Ling Chen, Ph.D. LCK 10/24/95

cc: NDA 20-805; HFD-180(Clinical Review); HFD-426(Fleischer); HFD-427 (MLChen, Colangelo), HFD-340(Viswanathan); Chron; Drug; Reviewer; HFD-19 (FOI)

APPENDIX 1:

STUDY SUMMARIES

1. Study _____. "A STUDY TO INVESTIGATE THE RELATIVE BIOAVAILABLITY OF ODANSETRON SYRUP AND ZOFRAN TABLETS 4MG"

Volumes: 6 of 6 **Pages:** 6-1 to 6-181

Investigator & Location: - - - —

Study Dates: 1/17/94 to 1/24/94

Objective:

To evaluate the bioequivalence of odansetron 4mg/5ml oral solution relative to that of ondansetron 4mg tablets (Zofran®) in healthy adult male volunteers.

Formulations:

Odansetron 4mg/5ml solution - contains 4mg of ondansetron as ondansetron hydrochloride dihydrate per 5ml (see **Appendix 2** for quantitive composition and certificate of analysis); Production Batch . supplied as glass amber bottles each containing 60ml of solution.
Odansetron 4mg tablets (Zofran®) - white film coated tablets; Batch . the tablets used for this study were taken from a production batch of the U.S. market image formulation (see **Appendix 2** for quantitive composition and certificate of analysis).

Methods:

This was a randomized, open-label, two-way crossover study to evaluate the bioequivalence of ondansetron 4mg/5ml oral solution to that of the market image 4mg tablet in 16 healthy male subjects. Each subject received a single 4mg dose of the tablet or the oral solution on two separate occasions with a 7 day interval between the dosing occasions. The solution was administered with an oral syringe and both doses were administered with 100ml of water. In addition, each volunteer drank 200ml of water upon rising and another 200ml at 2 hours postdose. The subjects fasted for at least 8 hours prior to and for 4 hours after dosing.

Plasma samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours postdose for determination of ondansetron plasma concentrations.

Assay:

***NOTE: Only the Performance Report was provided in this submission; the Validation Report was missing. The Performance Report, including all plasma concentration data, is provided in Appendix 2.**

Sensitivity:

Specificity:

Quality Control Precision and Accuracy:

for Subjects #7 and 8).

The sponsor noted the failure of this but accepted the data on the basis that (1) most of the ondansetron concentrations were less than (2) the was acceptable up to (the second highest standard), and (3) . Re-assay of the samples from these two subjects was apparently not possible because of insufficient sample volume. From a total of 52 concentration determinations from these two subjects, 5 concentrations were found to be greater than with the highest at for Subject #8. According to the sponsor, these higher values were the result of the insufficient sample volume effects on the final concentration determinations. The sponsor concluded that the data for Subjects #7 and 8 were acceptable since most of the data, i.e., 47 of a total of 52 determinations, were in the range covered by the successful QC samples.

Data Analysis:

Cmax & Tmax - directly from the data;
AUCinf - linear trapezoidal approximation with extrapolation to infinite time;
λ_z - linear regresson of log-linear portion of the curve;
T½ - $(\ln 2)/\lambda_z$;
Statistics - standard ANOVA of log-transformed Cmax, AUCinf, and T½ data and of untransformed Cmax, AUCinf, Tmax, λ_z, and T½. The 90% confidence intervals were constructed using the two one-sided test for log-transformed AUCinf and Cmax ratios (solution/tablet) and the standard bioequivalence acceptance criteria was used (i.e., within 80-125% for each); 95% confidence

intervals were also constructed for the parameters.

Results:

The median plasma ondansetron concentrations for the 16 male subjects receiving the 4mg/5ml oral solution and the 4mg tablet are illustrated in Figure 1 and the individual concentration-time data are provided in Table 1 of the Assay Performance Report in **Appendix 2**. The individual values and summary statistics for the pharmacokinetic parameters are given in Tables 1 through 5. The results of the statistical analyses are provided in Table 6. The 90% confidence intervals for log-transformed AUCinf and Cmax ratios were (91%,120%) and (82%,109%), respectively. No statistical differences were detected in the respective median and mean values for Tmax and T½. There were no serious adverse events reported in this trial.

As shown in Table 7, the extrapolated AUC (i.e., C_{last}/λ_z) accounted for greater than 20% (up to 40%) of the total AUCinf in 6 subjects (i.e., 8 out of 32 total determinations). The sponsor noted that since the plasma ondansetron concentrations at the last timepoint (i.e., at 16 hrs) was below the lower limit of quantification for 5 of these 6 subjects, extending the sampling period beyond 16 hours apparently would not have decreased the extrapolated AUC. The sponsor also noted that the estimates of λ_z and/or T½ were consistent with those obtained previously. Inspection of previous pharmacokinetic data by this reviewer verified this statement.

The assessment of bioequivalence between the two formulations included the pharmacokinetic data from Subjects 7 and 8. As previously mentioned in the **Assay** section above, the standard curve for these two subjects failed to meet the acceptance criteria for accuracy for the high level quality control samples (i.e., The acceptance criteria internally set by the sponsor was at for the high QC samples, which is more stringent than that generally used at the present time, i.e., for all levels of QC samples (REF: *Shaw VP, et.al. Pharm. Res. 9(4): 588-592, 1992*). If the currently accepted criterion of is applied to the performance of the high QC samples for this then 1 out of the 2 determinations pass, and consequently the entire would also pass.

If the data from these two subjects are omitted from the bioequivalence assessment this reviewer obtained the following results:

N = 14	AUCinf (ng.h/ml)			Cmax (ng/ml)	
	Solution	*Tablet*		*Solution*	*Tablet*
Geometric Mean	46.3	43.0		7.08	7.31
Arithmetic Mean	49.1	46.8		7.57	7.96
S.D.	17.6	18.1		2.85	3.20
C.V. (%)	35.9	38.6		37.7	40.2
90% Conf. Interval (2 one-sided test)	(92.5%,125.0%)			(82.7%,113.3%)	

Conclusions:

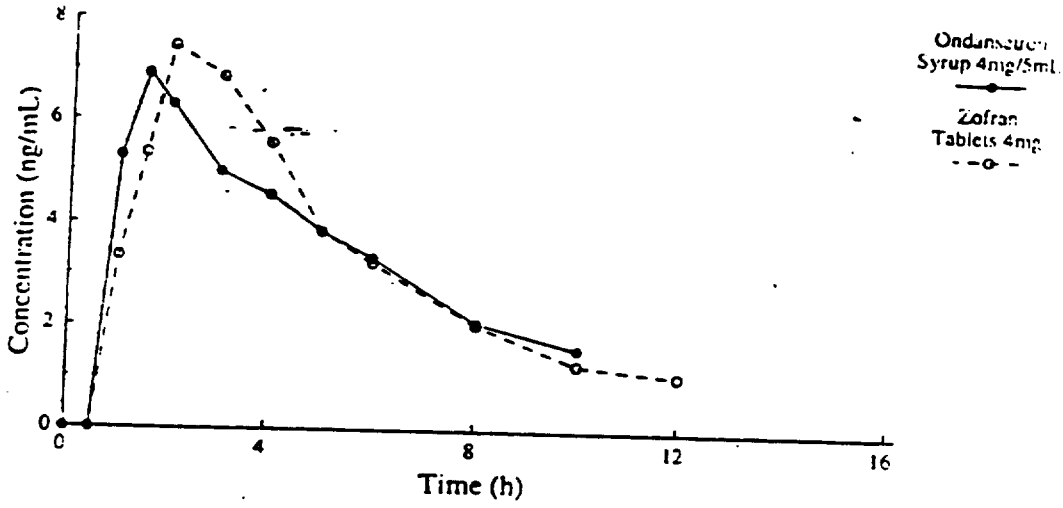
The results indicated that the 4mg/5ml oral solution dose was bioequivalent to the 4mg tablet dose in the 16 healthy adult males studied.

Despite the fact that the contribution of the extrapolated AUC to the total AUCinf was greater than 20% (up to 40%) in 6 subjects, the sponsor concluded this did not have a significant impact on the outcome of this study. While this conclusion may be true, it is recommended that the sponsor perform an additional bioequivalence assessment using the AUC from time zero to the last quantifiable plasma ondansetron concentration (i.e., AUC(0-LQC)).

The inclusion of the pharmacokinetic data from the two subjects (i.e., #7 and #8) in whom the
acceptable since: (1) most of the concentration data, i.e., 47 of a total of 52 concentration determinations, were in the range covered by the successful low and medium level quality control samples, (2) if the currently used assay performance criterion of is applied to the performance of the high QC samples, instead of the more stringent criterion internally set by the sponsor (i.e., then the entire would pass, and (3) re-assessment of bioequivalence after omission of the pharmacokinetic data from these two subjects indicated that the oral solution remained bioequivalent to the tablet formulation.

11. FIGURES

Figure 1 Median Ondansetron Plasma Concentration-Time Profiles



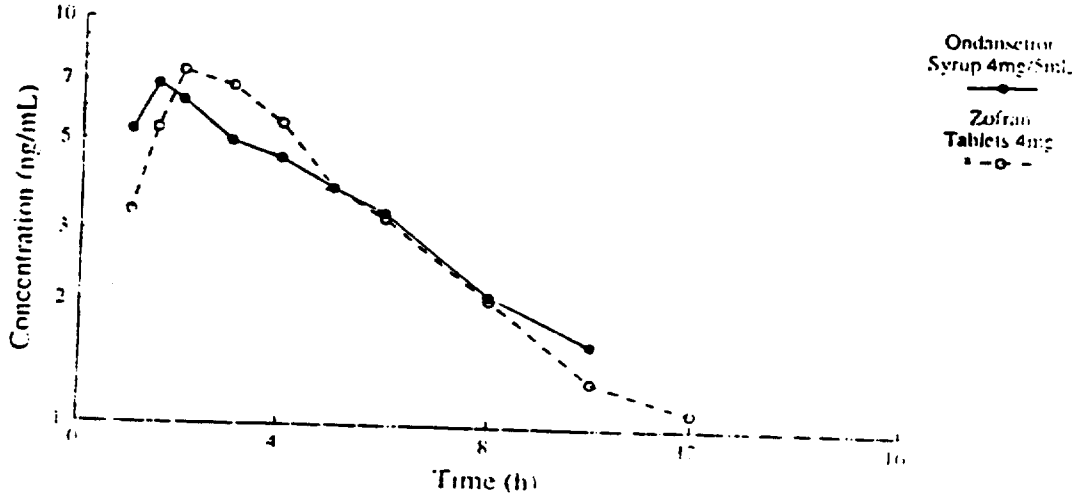


TABLE 1 AUC_{∞} (ng.h/mL) VALUES FOR EACH SUBJECT AFTER ADMINISTRATION OF ONDANSETRON SYRUP 4mg/5mL AND ZOFRAN TABLETS 4mg ON SEPARATE OCCASIONS TO SIXTEEN HEALTHY MALE VOLUNTEERS.

Subject Number	Sequence	Treatment A	Treatment B	Difference A - B	Ratio A/B	Log Ratio Ln A/B
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Median		52.2	49.9	1.7	1.02	0.0194
Minimum		25.8	17.7	-14.3	0.65	-0.4294
Maximum		124.5	122.5	22.3	2.26	0.8153
Arithmetic mean		53.2	52.0			
SD		25.2	25.3			
CV		47.4	48.7			
Geometric mean		48.8	46.6			
Mean of logs		3.89	3.84			
SD of logs		0.42	0.49			

Treament A : Ondansetron Syrup 4mg/5mL

Treatment B : Zofran Tablets 4mg

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TABLE 2 C_{max} VALUES (ng/mL) FOR EACH SUBJECT AFTER ADMINISTRATION OF ONDANSETRON SYRUP 4mg/5mL AND ZOFRAN TABLETS 4mg ON SEPARATE OCCASIONS TO SIXTEEN HEALTHY MALE VOLUNTEERS.

Subject Number	Sequence Treatment A	Treatment B	Difference A - B	Ratio A/B	Log Ratio Ln A/B
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
Median	7.6	8.9	-0.6	0.95	-0.0550
Minimum	3.6	3.1	-3.4	0.65	-0.4238
Maximum	12.5	13.1	3.9	2.26	0.8145
Arithmetic mean	7.9	8.5			
SD	2.9	3.4			
CV	36.7	40.0			
Geometric mean	7.42	7.82			
Mean of logs	2.00	2.06			
SD of logs	0.39	0.45			

Treament A : Ondansetron Syrup 4mg/5mL.

Treatment B : Zofran Tablets 4mg.

TABLE 3 t_{max} (h) VALUES FOR EACH SUBJECT AFTER ADMINISTRATION OF ONDANSETRON SYRUP 4mg/5mL AND ZOFRAN TABLETS 4mg ON SEPARATE OCCASIONS TO SIXTEEN HEALTHY MALE VOLUNTEERS.

Subject Number	Sequence	Treatment A	Treatment B	Difference A - B	Ratio A/B	Log Ratio Ln A/B
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Arithmetic mean		2.2	2.3			
SD		1.2	1.2			
CV		54.5	52.2			
Geometric mean		2.0	2.0			
Mean of logs		0.64	0.69			
SD of logs		0.51	0.52			

Treament A : Ondansetron Syrup 4mg/5mL.

Treatment B : Zofran Tablets 4mg.

TABLE 4 $t_{½}$ (h) VALUES FOR EACH SUBJECT AFTER ADMINISTRATION OF ONDANSETRON SYRUP 4mg/5mL AND ZOFRAN TABLETS 4mg ON SEPARATE OCCASIONS TO SIXTEEN HEALTHY MALE VOLUNTEERS.

Subject Number	Sequence	Treatment A	Treatment B	Difference A - B	Ratio A/B	Log Ratio Ln A/B
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Median		3.7	3.8	0.2	1.06	0.059
Minimum		2.1	2.0	-2.8	0.44	-0.829
Maximum		8.2	8.4	1.8	1.59	0.466
Arithmetic mean		4.0	4.2			
SD		1.7	1.8			
CV		42.5	42.9			
Geometric mean		3.75	3.89			
Mean of logs		1.32	1.36			
SD of logs		0.38	0.41			

Treament A : Ondansetron Syrup 4mg/5mL

Treatment B : Zofran Tablets 4mg.

TABLE 5 λ_z (1/h) VALUES FOR EACH SUBJECT AFTER ADMINISTRATION OF ONDANSETRON SYRUP 4mg/5mL AND ZOFRAN TABLETS 4mg ON SEPARATE OCCASIONS TO SIXTEEN HEALTHY MALE VOLUNTEERS.

Subject Number	Sequence	Treatment A	Treatment B	Difference A - B	Ratio A/B	Log Ratio Ln A/B
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Arithmetic mean		0.2000	0.2000			
SD		0.1000	0.1000			
CV		50.0000	50.0000			
Geometric mean		0.1848	0.1781			
Mean of logs		-1.6884	-1.7254			
SD of logs		0.3836	0.4098			

Treament A : Ondansetron Syrup 4mg/5mL

Treatment B : Zofran Tablets 4mg

Table 6

A summary of the pharmacokinetic parameters for ondansetron together with the statistical analysis are shown below:

Parameter	Treatment	Estimate	95% CI	Mean Ratio	90% CI	p-value
AUC_∞ (ng h/mL)	A	48.8	43.3, 54.9			
	B	46.6	41.4, 52.5	105%	91%, 120%	0.573
C_{max} (ng/mL)	A	7.42	6.57, 8.38			
	B	7.82	6.92, 8.83	95%	82%, 109%	0.521
t_{max} (h)	A	2.00	1.00, 5.00			
	B	2.00	1.00, 5.00	0.00	-0.50, 0.50	0.872
$t_{½}$ (h)	A	3.75	3.29, 4.27			
	B	3.89	3.42, 4.43	96%	83%, 112%	0.663

Data are presented as geometric means and 95% confidence intervals except for t_{max} which is presented as median and range. The mean ratio is presented as the ratio of Treatment A to Treatment B with the 90% confidence intervals with the exception of t_{max} which is presented as the median difference with the 90% confidence intervals.

Treatment A : Ondansetron Syrup 4mg/5mL.

Treatment B : Zofran Tablets 4mg.

TABLE 7 VALUES OF %AUC_{∞} EXTRAPOLATED FOR EACH SUBJECT.

Subject Number	Sequence	Treatment A	Treatment B
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
Median		17.1	15.0
Minimum		7.5	5.7
Maximum		39.9	34.9
Arithmetic mean		18.8	15.7
SD		9.4	7.8
CV		50.0	49.7

Treament A : Ondansetron Syrup 4mg/5mL.

Treatment B : Zofran Tablets 4mg.

PREVIOUS BIOPHARMACEUTICS REVIEWS:

STUDIES AND

II. PHARMACOKINETIC STUDIES

A. RELATIVE BIOAVAILABILITY STUDY

TITLE: AN EVALUATION OF THE PHARMACOKINETICS OF ONDANSETRON (GR 38032F) IN HEALTHY MALE VOLUNTEERS AFTER 8 MG ORAL DOSES, ONE TABLET AND ONE SOLUTION. (PROTOCOL # VOL. 5 pp. 038.

INVESTIGATOR:

OBJECTIVES:
1. To evaluate the relative bioavailability of oral ondasetron in healthy male volunteers given a tablet or solution of ondansetron as a single dose of 8 mg.

SUBJECTS:
Twenty-four healthy male subjects took part in the study. Their age ranged from 18 to 40 years old and their weight from 134 to 198 lbs. Inclusion and exclusion criteria were adequately described.

DRUG SUPPLIES:
1. Ondansetron 8 mg tablets (BATCH #
2. Ondansetron injection solution (2 mg/mL) BATCH #

STUDY DESIGN AND DOSAGE ADMINISTRATION:
The study was an open-label, randomized cross-over study. Each subject received 8 mg ondansetron orally, either as a tablet or as a solution after an overnight fast. The tablet was ingested with 240 mL of water, whilst 4 mL of ondansetron solution from a 2.0 mg/mL ampoule was added to 120 mL of water, ingested and a further 116 mL of water was used to rinse the dosing cup and the rinse solution swallowed. The subjects were allowed food five and ten hours post-administration of the drug. There was a wash-out period of one week between treatments.

Collection of biological samples:
Six mL blood samples were collected using venipuncture into a heparinized blood collection tubes at 0, 5, 15, 30, 45, 60, 75 90 minutes and 1.75 2.0, 2.5 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24 hours post-dosing. Ten mL urine samples were collected immediately prior to and at the intervals 0-4, 8-12 and 12-24 hours post-dosing. The urine samples were not analyzed for this study.

ANALYTICAL METHODOLOGIES:
An method (previously validated for ondansetron IV)

PHARMACOKINETIC RESULTS:

Using GLM procedure for ANOVA statistical comparison of T_{max}, C_{max} and $AUC_{0-\infty}$ were made with consideration to subject, period and treatment. There was no significant difference in these parameters between the solution and tablet of ondansetron. The coefficient of variance ranged for the pharmacokinetic parameters ranged from 26.5 to 34.6%). The relative bioavailability of the tablet compared to the solution was 103.1 ± 20.3%. The pharmacokinetic parameters are summarized in Table 1 below. The power, 90% confidence intervals and conclusion for the two one-sided tests are presented in Table 2.

Table 1. SUMMARY OF PHARMACOKINETIC PARAMETERS AND STATISTICS

Parameter	Tablet (±S.D.)	Solution (±S.D.)	p values
AUC ng.h/mL	166.0 (44.2)	167.3 (57.9)	0.8603
%C.V.	26.60	34.60	
C_{max} ng/mL	26.3 (7.0)	27.7 (8.4)	0.1743
%C.V.	26.50	30.20	
T_{max} h	1.79 (0.58)	1.70 (0.54)	0.5071
%C.V.	32.31	31.90	

Table 2. SUMMARY OF POWER, CONFIDENCE LIMITS AND TWO ONE-SIDED TESTS

Parameter	Power %	%Confidence Interval	2 One-sided
C_{max}	99.95	88.90-100.99	BE
AUC	99.03	91.73-106.71	BE
T_{max}	64.72	91.31-119.28	BE

CONCLUSIONS:

1. The statistical ANOVA showed no significant difference in the mean pharmacokinetic parameters between the oral solution and tablet of ondansetron.

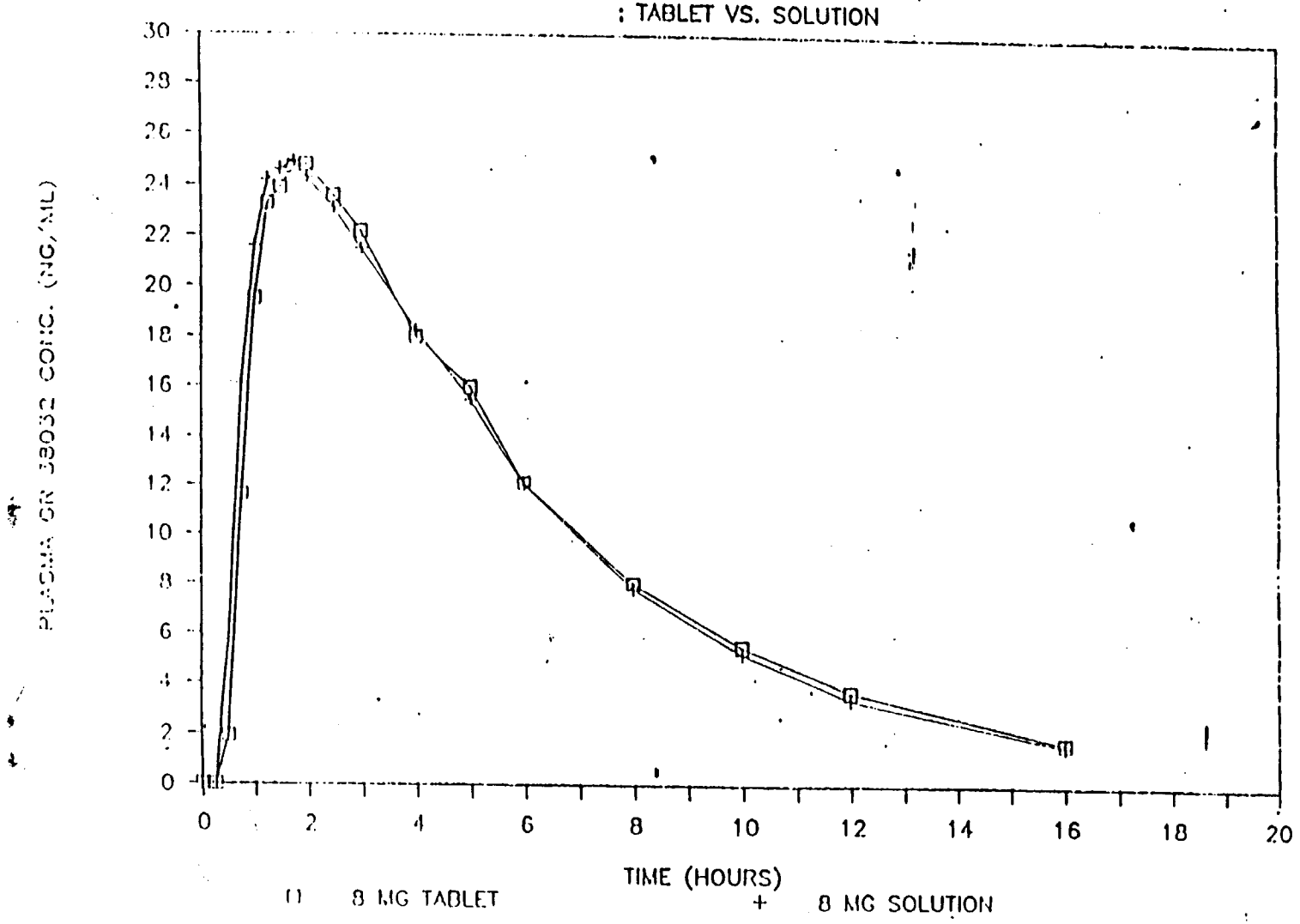
2. The relative bioavailability of ondansetron 8 mg tablet to 8 mg oral solution was 103.1 % in this single dose study.

3. Ondansetron 8 mg tablet is bioequivalent *in vivo* to ondansetron 8mg as an oral solution.

FIGURE 1

MEAN PLASMA CONCENTRATIONS

: TABLET VS. SOLUTION



C. DOSE PROPORTIONALITY STUDY

TITLE: AN EVALUATION OF THE STEADY STATE PHARMACOKINETICS OF ONDANSETRON AFTER 1,4 AND 8 MG ORAL DOSES (PROTOCOL # VOL. 6 pp. 001

INVESTIGATOR:

OBJECTIVES:

1. To determine whether ondansetron pharmacokinetic parameters are dose proportional between 1 and 8 mg.

2. To determine whether the accumulation of drug at steady-state is predictable from single-dose pharmacokinetics.

3. To evaluate any circadian variation in steady-state pharmacokinetic parameters over the three dosing intervals of a q8h oral dosing regimen.

SUBJECTS:

Twenty-five, healthy male subjects were entered into the study. Their age ranged from 19 to 36 years old (mean=25.5) and their weight from 140 to 200 lbs (±15% of their ideal weight). Inclusion and exclusion criteria were adequately described.

DRUG SUPPLIES:

1. Ondansetron 1 mg tablets (BATCH #
2. Ondansetron 4 mg tablets (BATCH #
3. Ondansetron 8 mg tablets (BATCH #

STUDY DESIGN AND DOSAGE ADMINISTRATION:

The study was an open-label, randomized cross-over study. Each subject received ondansetron orally either as 8 mg, 4 mg, or 1 mg doses q8h for 7 doses (1 mg or 4 mg) or 9 doses (8 mg). There was a minimum of three days wash-out period between treatments. Subjects fasted overnight before each treatment period and for three hours after the first dose during each treatment period. Each tablet was ingested with 240 mL of water at room temperature. Standardized meals were served at the same time for each treatment period. Food and beverages were consumed not less than 1 hour prior to dosing and within 2 hours post-dosing. Coffee, tea and other xanthine-containing beverages and foods were disallowed during the study.

Subject # 13 was dropped from the study after the first treatment phase due to family illness and was replaced by subject # 25.

Collection of biological samples:
Six mL blood samples were collected using venipuncture into heparinized blood collection tubes at 0, 30, 60 and 90 minutes and 2, 3, 4, 5, 6 and 8 hours, after the 1st and 7th doses for the 1 mg and 4 mg dosing regimens. In addition blood samples were collected at 0, 30, 60 and 90 minutes and 2, 3, 4, 5, 6 and 8 hours after the 8th and 9th doses for the 8 mg dosing regimen. Also, blood samples were collected immediately before doses 4 and 5, and at times 10, 12 and 16 hours after the last dose of each treatment period. Ten mL urine samples were collected at the time interval 0 -8 hours following the 7th dose for the 1 mg and 4 mg dosing regimens and in addition, 0-8 hours following the 8th and 9th doses for the 8 mg dosing regimen. Urine samples were not analyzed for this report.

ANALYTICAL METHODOLOGIES:
Plasma samples were analyzed by means of an
The method had been validated for NDA 20-0007 IV ondansetron).
but no graphical data was presented.

PHARMACOKINETIC RESULTS:
Using GLM procedure for ANOVA, statistical comparison of C_{max}, T_{max}, k_e and AUC_{inf} were made with consideration to subject, period and treatment and are normalized to the 8 mg dosage.

Statistical Summary - Dose proportionality:

PARAMETER	P VALUE FIRST DOSE	SIGNIFICANT PAIRS	P VALUE 7TH DOSE	SIGNIFICANT PAIRS
*$NAUC_{0-\infty,1}$	0.002	(1MG,8MG)	-	-
*$NC_{MAX,1}$	0.001	(1MG,8MG) (4MG,8MG)	-	-
$T_{MAX,1}$	NS	-	-	-
$K_{E,1}$	NS	-	-	-
*$NAUC_{0-8H,SS}$	-	-	NS	
*$NC_{MAX,SS}$	-	-	0.0014	(1MG,8MG) (4MG,8MG)
$T_{MAX,SS}$	-	-	0.0059	(1MG,4MG) (1MG,8MG)
$K_{E,SS}$	-	-	0.0059	(1MG,4MG) (1MG,8MG)

*NORMALIZED TO 8 MG

The results are found in Tables 2 to 5 (see Appendix, taken from vol. 6, pp. 27-30). The

results show that there is non-proportionality between the different dosages after the first dose, since there is significant difference in the dose-normalized values of $C_{max,1}$ ($p=0.001$) between 1 mg and 8 mg and $AUC_{inf,1}$ ($p=0.002$), but not between 4 mg and 8 mg. There is no statistical difference for $T_{max,1}$ ($p=0.3$) and the elimination rate constant ($p=0.971$) for the first dose.

The firm points out that there are many values in the data analyzed for the 1 mg and 4 mg dose that fall below the limits of the assay, which will affect AUC_{inf} calculations. These values were counted as zero in calculations.

A significant period effect was noted for AUC_{inf} ($p=0.015$).

Paired t-test comparisons of trough levels analyzed at the 3rd and 6th dose show no significant difference between the three doses ($p>0.05$), showing that steady-state conditions were in effect. (Tables 6 to 8).

Dose proportionality was also investigated at steady-state, using ANOVA-GLM statistical procedure. (Tables 9 to 12). The AUC_{ss} showed no significant difference between the three doses ($p=0.1086$). C_{max} was significantly different for all doses ($p=0.0014$), however T_{max} and the mean elimination constant for the 1 mg dose were significantly different from the results for the higher doses ($p=0.0059$ and $p=0.001$ respectively). The firm noted that the elimination constant was calculated after the 7th dose for the lower strengths (1 mg and 4 mg), but after the 9th dose for the 8 mg dose. There were no sequence nor period effects shown. The 7th dose was given between 7.30 to 7.51 am, whilst the 9th dose was given between 11.30 and 11.51 pm. These differences led the firm to investigate the possibility of diurnal variations as having some influence.

Summary of Statistical Results:

PARAMETER	PAIRED T-TEST, P VALUE (1ST DOSE VS. 7TH DOSE)		
	1MG	4MG	8MG
C_{MAX}	0.0001	0.0001	0.0001
T_{MAX}	0.1024	0.1855	0.0008
**AUC	0.0008	0.0001	0.0412
K_E	0.2214	0.0001	0.0001*

**AUC = $AUC_{0-\infty}$ FOR 1ST DOSE, AUC_{ss} FOR 7TH DOSE
*1ST DOSE VS. 9TH DOSE

The possibility of diurnal variations was investigated by comparing pharmacokinetic parameters of the highest dosage strength (8 mg) at the different dose times, ie the 7th, 8th and 9th dose intervals were compared statistically using GLM-ANOVA statistical routine and Duncan's multiple range test as a *post hoc* test of the difference.

AUC_{ss} for the 7th (7.00 am to 3.00 pm) dose was significantly higher than for the other dosing intervals (8th = 3.00 pm to 11.00 pm, 9th=11.00 pm to 7.00 am). $T_{max,ss}$ occurred significantly earlier in the 7 th dose than the later doses (8 th and 9 th); p=0.0008. Also, $C_{max,ss}$ was significantly higher for the 7 th dose than the later doses; p=0.0001.

Food intake was at 9.30 am, 11.30 am, 4.30 pm and 10.30 pm. The intake of food was not at a consistent interval in relation to dosing of ondansetron.

The firm stated that the differences in the pharmacokinetic parameters are due to diurnal effects taking place. However a food effect may also be contributing to this observation.

Summary of mean values:

Dosage	Cmax (ng/mL)	Tmax (h)	nCmax* (ng/mL)	AUC** (ng.h/mL)	nAUC* (ng.h/mL)	Half-life (h)
1 mg						
Dose #1	3.0	2.1	24.3	18.4	147.0	3.28
(%CV)	(31.7)	(32.0)	(31.7)	(51.7)	(51.7)	
Dose #7	4.6	1.9	36.6	23.6	188.9	3.54
(%CV)	(30.8)		(30.8)			
4 mg						
Dose #1	13.8	2.1	27.5	83.5	166.9	3.24
(%CV)	(32.3)	(31.4)	(31.7)	(51.7)	(35.7)	
Dose #7	19.7	1.8	39.4	98.9	197.7	4.05
(%CV)	(35.0)		(35.0)			
8 mg						
Dose #1	30.9	1.9	30.9	186.4	186.4	3.25
(%CV)	(33.0)	(31.7)	(33.0)	(36.4)	(36.4)	
Dose #7	42.8	1.5	42.8	204.8	204.8	
(%CV)	(32.1)		(32.1)			
Dose #8	37.1	1.9		177.6		
(%CV)	(34.7)	(37.5)		(33.2)		
Dose #9	33.1	2.1		169.8		4.47
(%CV)	(32.6)	(39.8)		(34.8)		

* normalized to 8 mg dose, ** Dose #1 - AUC[inf]; Dose #7,8,9 - AUC[ss]

Linear regression on the AUC_{ss} values for 1 mg , 4 mg and 8 mg dosage strengths and after the 7th dose gave r=0.9999.

The Accumulation Index can be expressed as:

Dosage Strength	Accumulation Index $C_{max,ss}/Cmax_{max,1}$
1mg	1.53
4mg	1.43
8mg	1.39

The values of the accumulation index are close particularly for the 4mg and 8mg dose indicating -kinetics of ondansetron are similar in the dose range studied.

COMMENTS:

The parameters calculated for the 1mg dose are not satisfactory as most of the plasma drug levels were close to the lowest detectable concentration for the assay method. Also, the drug is to be marketed in the 4 mg and 8 mg strength, therefore the 1 mg strength is not pertinent to this application.

CONCLUSIONS:

1. The statistical results showed that there was no difference between the trough levels on the 4th and 7th doses i.e. steady-state was in effect.

2. The firm said there was evidence of dose accumulation when AUC_{inf} were compared, but not for AUC_{ss} values. There was evidence of dose accumulation at steady-state when the elimination half-life, C_{max} and T_{max} were compared. But dose accumulation was not in evidence at steady-state between 4 mg and 8 mg except for C_{max} values.

3. Calculation of linear regression coefficient for the AUC's at steady state showed that ondansetron was dose proportional between doses of 1 mg to 8 mg. Comparison of the AUC_{0-8h} at steady state and normalized to the 8mg dose showed that there was no statistical difference for all strengths and hence ondansetron was dose proportional between 4 and 8 mg.

4. There was marginal evidence of dose accumulation as shown by the accumulation index using $C_{max's}$.

APPENDIX 2

5 Page(s) Redacted

5. Evidence of diurnal variations in the was confounded by food intake being different for the different doses taken during each day.

6. Evidence of dose accumulation was not supported by study # where 8 mg tid was administered for 17 doses after an initial single dose.

7. The multiple dose study was not conducted according to the dosage regimen in the proposed labeling. The labeling implies that ondansetron would be given as 8mg every four hours on the first day for the first three doses and then 8 mg tid for subsequent days. The firm sent simulations of various dosing regimens to the Medical Division in which mean parameters and parameters for the worst case ie. smallest volume of distribution, fastest absorption rate and slowest elimination rate found in the study population. Although the regimen 8 mg every four hours was shown figuratively using for the mean parameters, the data was not tabulated as with the other regimens and the worst case data was not presented. The reviewer used these worst case parameters to simulate data for 8 mg taken every four hours for three doses and then up to seven doses (which would then be at steady-state). All of these simulations assume linear kinetics. The firm's simulations and the reviewer's are attached to the information for this study.

Results from simulations of 8 mg oral dose:

No. of Doses	Dosing Interval	C_{max} ng/ml	C_{min} ng/ml	C_{avg} ng/ml
n=3	4 hourly	97.01	66.92	112.06
	8 hourly	73.96	31.19	56.03
n=7	4 hourly	121.73	83.98	112.06
	8 hourly	77.96	32.88	56.03

Worst case parameters: ka=3.55h^{-1}, ke=0.123h^{-1}, Vd=145.1L

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NDA: 20-605 **Submission Date:** October 10, 1995

Zofran® (Ondansetron Hydrochloride Dihydrate) Oral Solution, 4mg/5ml
(±)-1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride dihydrate

Sponsor: Glaxo Wellcome Inc.
Research Triangle Park, NC

Type of Submission: Sponsor's response to request from OCPB

OCPB Reviewer: Philip Colangelo, Pharm.D., Ph.D.

The sponsor submitted additional information regarding bioequivalence study "A Study to Investigate the Relative Bioavailability of Ondansetron Syrup and Zofran Tablets 4mg" at the request of this OCBP reviewer. The request was conveyed to the sponsor through the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and appeared in the OCPB review of NDA 20-605 as follows:

Comments To Be Sent To Sponsor:

1. The contribution of the extrapolated AUC to the total AUCinf was >20% (up to 40%) for several subjects (i.e., 6 subjects, or 8 out of a total of 32 determinations) in Study Therefore, it is recommended that the sponsor perform a re-assessment of bioequivalence of the 4mg/5ml solution and the 4mg tablet using the AUC from time zero to the last quantifiable plasma ondansetron concentration, i.e., AUC(0-LQC), in addition to that already performed using AUCinf.

Sponsor's Response:

In this current submisson, the sponsor provided estimates of AUC calculated from time 0 to the last measured interval, i.e., AUClast, and also the previously calculated estimates of AUCinf for comparison (see **Attachment 1**). The standard ANOVA and 90% confidence interval, using the 2 one-sided tests, were performed on the log-transformed AUClast data (i.e., mean ratio of oral solution/tablet).

The arithmetic mean(±SD) estimates for AUClast were 44.2±22.3 ng.h/ml for the 4mg ondansetron oral solution dose and 43.2±21.7 ng.h/ml for the 4mg tablet dose. No significant sequence or period effects were detected in the ANOVA ($p > 0.05$; see **Attachment 2, Tables 1 and 2**). However, the 90% confidence interval for AUClast (86%, 128%) was slightly outside the upper limit of the acceptance criteria for bioequivalence (i.e., 80% to 125%), but the 90% confidence interval for AUCinf (91%, 120%) fell within the acceptance range (see **Attachment 2, Tables 3 and 4**). As mentioned above, the contribution of the extrapolated AUC (i.e, C_{last}/λ_z) to the total AUCinf was >20% (up to 40%) for several subjects in study see **Attachment**

2, Table 5).

The issue was whether to accept AUCinf or AUClast as the more appropriate bioequivalence estimate of the extent of ondansetron absorption. The sponsor noted that since the plasma ondansetron concentrations at the last timepoint (i.e., at 16 hrs) was below the lower limit of quantification for 5 of these 6 subjects, extending the sampling period beyond 16 hours apparently would not have decreased the extrapolated AUC. The sponsor also noted that the estimates of λ_z and/or T½ were consistent with those obtained previously. Inspection of previous pharmacokinetic data by this reviewer verified this statement. Furthermore, inspection of the semi-log plots of ondasetron concentration *vs* time data for study revealed that the terminal phase rate constant, λ_z, was determined from the log-linear portion of the curves using at least 4 data points (mean number of data points ~5 for both treatments) for all subjects.

In conclusion, these results indicated that AUCinf was appropriate to use in this study for the evaluation of the extent of ondansetron absorption.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the additional data provided by the sponsor for bioequivalence study ' of NDA 20-605 and found this information to be acceptable. No further information is needed.

Philip M. Colangelo 10/24/95
Philip Colangelo, Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by Lydia Kaus, Ph.D. LCK 10/24/95

FT Initialed by Lydia Kaus, Ph.D. LCK 10/24/95

cc: NDA 20-605; HFD-180(Clinical Review); HFD-880(Fleischer); HFD-870(ML Chen, Colangelo), HFD-340(Viswanathan); Chron; Drug; Reviewer; HFD-19 (FOI)

ATTACHMENT 1

Glaxo

'axo Inc. Research Institute

October 10, 1995

DUPLICATE

ORIG AMENDMENT

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 I
Food and Drug Administration
HFD-180, PKLN, 6B-24
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-605; Zofran® (ondansetron hydrochloride) Oral Solution
Response to FDA Request/Comment

Dear Dr. Fredd:

In response to a request received during a September 27 ,1995, telecon with Ms. Kati Johnson of the Division, we are amending our New Drug Application for Zofran Oral Solution to provide additional information regarding bioequivalence study A Study to Investigate the Relative Bioavailability of Ondansetron Syrup and Zofran Tablets 4mg.

This information consists of:

1) concentration time/pharmacokinetic data, including AUC calculated from:
   - zero to last measured interval
   - zero to infinity

2) statistical data on SAS diskettes, including:
   - dataset item descriptions
   - method of statistical analysis
   - comparative plot of the AUC (infinity) values after administration of ondansetron syrup and Zofran Tablet

The requested information is contained on two diskettes, each submitted in duplicate. For the convenience of the reviewer, paper copies of SAS dataset item descriptions concentration time/pharmacokinetic data, the method of statistical analysis, the

comparative plot of the AUC (infinity) values, and statistical tables are also provided in duplicate.

Should you require further information, please contact me directly at (919) 990-6059.

Sincerely,

John West

John B. West
Manager, Regulatory Affairs

ATTACHMENT 2

TABLE 1. ANALYSES OF VARIANCE TABLES: LOG TRANSFORMED ANALYSES : LOOKING AT SEQUENCE EFFECTS WITH SUBJECT(SEQUENCE) AS THE ERROR TERM

AUC_{LAST} (NG.H/ML)

Source	df	ss	ms	F	p value
Sequence	1	1.4777	1.4777	3.30	0.091
Subject(Sequence)	14	6.2624	0.4473		

Type 3 sums of squares used

TABLE 2. ANALYSIS OF VARIANCE TABLES: LOG TRANSFORMED ANALYSES

AUC_{LAST} (NG.H/ML)

Source	df	ss	ms	F	p value
Subject	15	7.7401	0.5160		
Period	1	0.0028	0.0028	0.03	0.870
Treatment	1	0.0177	0.0177	0.18	0.681
Error	14	1.4027	0.1002		

Type 3 sums of squares used

TABLE 3 AUC_{LAST} (NG.H/ML): LOG TRANSFORMED ANALYSIS

Treatment	Geometric Mean#	95% CI
Ondansetron Syrup	39.4	(33.2, 46.6)
Zofran tablet 4mg	37.5	(31.7, 44.5)

Treatment Comparison	Estimate	90% CI	p value
Ondansetron Syrup / Zofran tablet 4mg	105%	(86%, 128%)	0.681

least squares means adjusted for design imbalance

TABLE 4 AUC_{∞} (NG.H/ML) : LOG TRANSFORMED ANALYSIS

Treatment	Geometric Mean#	95% CI
Ondansetron Syrup	48.8	(43.3, 54.9)
Zofran tablet 4mg	46.6	(41.4, 52.5)

Treatment Comparison	Estimate	90% CI	p value
Ondansetron Syrup / Zofran tablet 4mg	105%	(91%, 120%)	0.573

least squares means adjusted for design imbalance

TABLE 5 VALUES OF %AUC_{∞} EXTRAPOLATED FOR EACH SUBJECT.

Subject Number	Sequence	Treatment A	Treatment B
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
Median		17.1	15.0
Minimum		7.5	5.7
Maximum		39.9	34.9
Arithmetic mean		18.8	15.7
SD		9.4	7.8
CV		50.0	49.7

Treament A : Ondansetron Syrup 4mg/5mL.

Treatment B : Zofran Tablets 4mg.

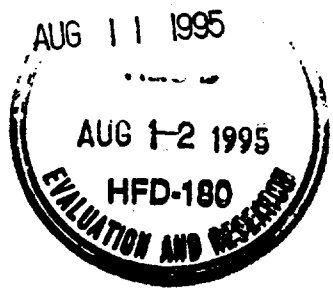
133 Page(s) Redacted

K. Johnson

Statistical Review and Evaluation

NDA #: 20-605

Date: AUG 11 1995



Applicant: Glaxo Wellcome Inc.

Name of Drug: Zofran (Ondansetron) Solution

Documents Reviewed:

NDA Submission, Amendment Chemistry, Manufacturing, and Controls, Section F and G, Date of Document, June 22, 1995.

Introduction

Glaxo Wellcome Inc. has submitted twelve months stability data to justify a 24-month expiration date for Zofran oral solution when stored upright between 15°C and 30°C. The reviewing CSO, Ms. Kati Johnson, HFD-180, has requested the Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data.

Sponsor's Designs and Analyses

The sponsor has submitted three batches stability data of Zofran oral solution 4mg/5mL. Results from up to 12 months stability testing of the oral solution at 2°C/AMBH, 30°C/60% RH, up to 6 months at 40°C/AMBH, and 1 month of light cabinet storage are submitted. Under all storage conditions, samples were stored horizontally to allow the oral solution to come in contact with the closure. Additional samples were stored vertically as spares and controls.

Samples have been tested for

The specifications for the variables of the drug product were listed in Table 1.

The sponsor indicated that all analyses were carried out in accordance with the FDA's "Guideline for Submitting Documentation for the Stability of Human drugs and Biologics" (February 1987). The SAS programs provided by the Division of Biometrics, Center for Drug Evaluation and Research, FDA, were used to estimate expiration dates.

The sponsor analyzed the stability data of ondansetron content, total impurities, over a period of twelve months under the storage conditions of 2°C/AMBH and 30°C/60%RH. Table 2 listed the final selected models and the predicted expiration dates for ondansetron content, total impurities, and content under 2°C/AMBH and 30°C/60%RH storage condition.

The least-squares regression lines and the corresponding two-sided 95% confidence limits for predicting mean ondansetron content, mean percentage of total impurities, and are given in Figures 1-6.

Based on the above analyses, the sponsor concluded that "the data generated on Zofran oral solution packed in amber glass bottles show excellent chemical and physical stability with the exception of external appearance of the pack where some leakage was observed in packs stored horizontally for an extended period. In addition, a small number of particles of benzoic acid were observed in the oral solution stored at 2°C/AMBH for 12 months. It is considered that Zofran oral solution will show excellent stability for up to 24 months when stored upright between 15°C and 30°C."

Reviewer's Analyses

The statistical procedures described in the FDA Guideline (February, 1987) were applied to the stability data provided by the sponsor. The reviewer analyzed the ondansetron content for Zofran oral solution 4 mg/5mL packaged in 60 mL amber USP type III glass bottles stored horizontally at 2°C/AMBH and 30°C/60%RH. The specification limits for ondansetron content are 95% to 105% of label claim. The statistical analyses and results are as follows:

a. Statistical analyses

(1) The ondansetron content stored at 2°C/AMBH.

Table 3 presents the data of batches stored at 2°C/AMBH and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the models with separate intercepts and common slope were selected. The 95% upper confidence bounds for the three regression lines were calculated.

(2) The ondansetron content stored at 30°C/60%RH.

Table 4 presents the data of batches stored at 30°C/60%RH and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the model with common intercept and common slope was selected. The 95% lower confidence bound for the regression line was calculated.

b. Results of analyses

Based on the above analyses, we found that the ondansetron content for Zofran oral solution 4 mg/5mL packaged in 60 mL amber USP type III glass bottles were stable after 18 months stored horizontally at 2°C/AMBH and 30°C/60%RH. Noted that the above estimated expiration dating period was based on the data extrapolation beyond the range of

storage time actually observed.

Summary

Glaxo Wellcome Inc. has requested an expiration date of 24 months for Zofran oral solution when stored upright between 15^{0}C and 30^{0}C.

The reviewer analyzed the data of ondansetron content for Zofran oral solution 4 mg/5mL packaged in 60 mL amber USP type III glass bottles stored horizontally at 2^{0}C/AMBH and 30^{0}C/60%RH. The statistical procedures described in the FDA Guideline (February, 1987) were applied to the stability data. Since the sponsor used the same statistical analyses and SAS programs to analyze the data of total impurities and sodium benzoate content, the reviewer did not analyze them again.

The above analyses results showed that the ondansetron content for Zofran oral solution 4 mg/5mL packaged in 60 mL amber USP type III glass bottles were stable after 18 months stored at 2^{0}C/AMBH and 30^{0}C/60%RH. Noted that the above estimated expiration dating period was based on the data extrapolation beyond the range of storage time actually observed.

Hence, the reviewer recommends that a 18 month expiry date be granted for Zofran oral solution when stored upright between 15^{0}C and 30^{0}C.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 8/11/95

Karl K. Lin, Ph.D., Group Leader, SARB

cc: NDA 20-605
HFD-180/Dr. Fredd
HFD-180/Dr. Gibbs
HFD-180/Dr. RFrankewich
HFD-180/Ms. K. Johnson
HFD-710/Chron
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-715/DRU 2.1.1, Zofran, Glaxo Wellcome Inc.

13 Page(s) Redacted

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Zofran
(ondansetron hydrochloride)

Oral Solution

NDA 20-605

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-180

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-605

Zofran (ondansetron hydrochloride) Solution

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Zofran Oral Solution, Glaxo, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31 a(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

In support of their new drug application, Glaxo has referenced the environmental assessment (EA) submitted in supplement 005 to NDA 20-007, which was approved on August 13, 1993. NDA 20-007/S-005 covered the drug substance (ondansetron hydrochloride) used in this application. The purpose of the present requested approval is for a new dosage form, an oral solution.

The applicant has calculated an MEEC for the drug substance based on the use of this compound which is independent of market volume and which relies on a comprehensive worst-case scenario.

The environmental fate and effects of the emitted substances are not expected to change with the proposed action. The proposed action will not threaten endangered species or historic places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

1/16/97
DATE

PREPARED BY
Raymond P. Frankewich, Ph.D.
Reviewing Chemist
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

1/16/97
DATE

DIVISION CONCURRENCE
Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

1/24/97
DATE

Concurred
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

CC:
NDA 20-605
HFD-180 Division File(s)
HFD-357/NSager
HFD-820/JGibbs
HFD-181/CSO MMcNe[illegible]
HFD-180/RFrankewic
HFD-180/EDuffy
R/D init.:EDuffy/1-1
RF/dob F/T 1-16-97/W[illegible]

Paperwork held pending receipt of official Submission Signed on FAX info
1/24/97

Johnson

NDA 20-605

Glaxo Wellcome Inc.
Attention: John West
Five Moore Drive, P.O. Box 13358
Research Triangle Park, NC 27709

JUL - 5 1995

Dear Mr. West:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zofran (ondansetron HCL) Oral Solution

Therapeutic Classification: Standard

Date of Application: June 22, 1995

Date of Receipt: June 23, 1995

Our Reference Number: 20-605

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 August 22, 1995 in accordance with 21 CFR 314.101(a).

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

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

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Johnson
drafted: kj/June 30, 1995
c:\wpfiles\cso\n\20605406.0kj
ACKNOWLEDGEMENT (AC)

Sincerely yours,

KJ 6/30/95

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-007
NDA 20-103
NDA 20-403
NDA 20-605

OCT -5 1995

Glaxo Wellcome Inc.
Attention: John West
Five Moore Drive, P.O. Box 13358
Research Triangle Park, NC 27709

Dear Mr. West:

We acknowledge receipt on August 14, 1995 of your August 11, 1995 corespondences to the following new drug applications notifying the Food and Drug Administration that the corporate name has been changed from Glaxo Inc. to Glaxo Wellcome Inc.:

NDA 20-007-Zofran (ondansetron hydrochloride) Injection
NDA 20-103-Zofran (ondansetron hydrochloride) Tablets
NDA 20-403-Zofran (ondansetron hydrochloride) Injection Premixed
NDA 20-605-Zofran (ondansetron hydochloride) Solution

Our records have been revised to reflect these changes.

Sincerely yours,

KJ 10/4/95

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

cc:
Original NDAs 20-007, 20-103, 20-403, 20-605
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/kj
DISTRICT OFFICE

drafted: /October 4, 1995/c:\wpfiles\cso\n\20007510.9kj
General Correspondence (change of corporate name)

NDA 20-605

Glaxo Wellcome, Inc
Attention: John West
Five Moore Drive, P.O. Box 13358
Research Triangle Park, NC 27709

JAN - 2 1996

Dear Mr. West:

Please refer to your pending June 22, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron) Oral Solution.

We have completed our review of the biopharmaceutics section of your submission and have the following comments and requests:

1. Please provide the assay validation report for Study entitled, 'A Study to Investigate the Relative Bioavailability of Ondansetron Syrup and Zofran Tablets 4 mg."

2. In future bioequivalence study, if dosage strengths are compositionally proportional, we recommend that you compare the equivalence of two formulations using the highest strength (or dose) at which dose proportionality has been demonstrated. In this way, extrapolation of the bioequivalence to a lower strength (or dose) sill have greater justification.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
DISTRICT OFFICE
drafted: kj/December 22, 1995
c:\wpfiles\cso\n\20605512.0kj
r/d Initials:SFredd 12/28/95

INFORMATION REQUEST (IR)

1/2/96

1 Page(s) Redacted

NDA 20-605

MAY 24 1996

Glaxo Wellcome Inc.
Attention: John West
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. West:

Please refer to your pending June 22, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron hydrochloride) Solution.

We have completed our review of the chemistry, manufacturing and controls section of your submission and request the following information:

I. DRUG SUBSTANCE

Please supply specific references (including volume and page numbers) to those sections of NDA 20-007 (Zofran Injection) and any approved supplements for information concerning the synthesis, composition, characterization, and purity of the drug substance.

II. DRUG PRODUCT

A. Please provide the acceptance specifications and methods for the active ingredient. This can be done by specific reference to NDA 20-007.

B. Regarding excipients:

1. Please identify the source of the compendial excipients that are used in the drug product.

2. Please indicate whether or not the compendial tests are being performed on every lot of each compendial excipient. If not, provide the procedure for evaluating the raw materials.

C. On the fourth page of the batch record fo you state that some "materials were not fully tested prior to being used for manufacturing and were passed on as 'Restricted Batches (RB)' by materials QC. The tests will be carried out and added when complete." Please provide a full explanation of the

process for receiving and qualifying raw materials for use in drug product batches. Please justify the use of a process which would allow raw materials to be used in drug product batches without being fully tested against their specifications.

D. The in-process controls described do not appear to address certain potential problems that could occur during the manufacturing process. Two such specific problems could be contamination of the drug product by miscellaneous particulates or chemical impurities (which could occur if the containers used to the drug product were not sufficiently cleaned) or 2) the possibility that a substance that does not belong in the drug product may mistakenly be substituted for one that does. Expounding on the latter situation, most of the ingredients of the drug product formulation are in the form of Adopt additional in-process specifications and tests that could indicate the occurrence of problems such as those described. Alternately, provide a justification as to why they are not necessary.

E. Regulatory Specifications and Methods:

1. Regarding Sampling:

   a. Please provide a full description of your sampling plan for the drug product including the number of samples taken, the amount taken per sample, and the sampling intervals for stated batch sizes.

   b. Please describe the specific conditions under which more than one test would be performed on the same bottle of drug product.

2. Clarify how the relative response factor (RRF), a term in the calculation of related impurity content (%w/w of claimed ondansetron content), is obtained.

3. The major impurity of the drug substance is and its concentration is determined using an alternate Although this substance is not quantitated using this method, it should be proven that this procedure is capable of separating it from ondansetron and the rest of the Related Impurities. If this has already been demonstrated in a previously approved application, provide specific reference where this information is located.

4. Regarding the of Ondansetron in Zofran Oral Solution:

   a. Please provide specific references to NDA 20-007 for information regarding validating method specificity and reproducibility.

   b. We note

5.

   a. Clarify whether solution density was used in the calculation of content in the method validation procedure. If it was, then specify how the density of the sample solutions was controlled and measured. If it was not, then it should be clarified how the content was calculated.

   b. Ruggedness, or reproducibility, of the procedure was demonstrated by two different experiments, one of which consisted of performing the

6. Please submit descriptions, or provide specific reference to an approved application, for the listed experiments conducted to confirm suitability of the following assays:

   a. For ondansetron content:

b. For related impurities content:

7.

a. Please state whether or not solution density was used in the calculation of ondansetron content in the method validation procedure. If it was, state how the density of the sample solutions was controlled and measured. If it was not, then clarify how the ondansetron content was calculated.

b. Ruggedness, or reproducibility, was demonstrated by two different experiments, one of which consisted of performing

8. Regarding the calculation of recovery in the

9. Regarding validation of the used for the determination of

a. The application states that the following experiments, which were used to validate the assay method for Zofran Injection, are content in Zofran Oral Solution".

In addition, please provide a specific reference to an approved application where the descriptions of these methods might be found.

b.

For each experiment in which one of the parameters mentioned above was held at an extreme level, actual quantitative data should be provided for resolution between the and determination

F. Container/Closure System:

1. We note that a procedure similar to Confirm that the inspection level is analogous to level II. Explain how each pallet is sampled; for example,

2. A procedure similar to is used to sample Confirm that the inspection level is analogous to level II. State exactly how each case is sampled; for example, the number of caps per case inspected. Specify the

III. ENVIRONMENTAL ASSESSMENT

A. On pg. 7 of Volume 3 of the submission, under the heading '5.1 Drug Substance Information', , an impurity from the manufacturing process for ondansetron hydrochloride, is incorrectly provided with the chemical structure of ondansetron hydrochloride itself. This error should be corrected.

B. Several species are mentioned in the Discharge Consent from (Attachment 2 to the Manufacturing Site EA for the Volume 3, pg. 225) that must either not be present at any detectable level, or must be present below some specified level. There are no results given, either in the application or in the Discharge Consent (Attachment 2) that indicate that these determinations were ever done, or that the amounts of the substances mentioned were ever monitored. These results should be provided, to the extent that they exist. If they do not exist, provide an explanation, and indicate how compliance with the conditions described above is monitored.

C. In the form documenting the audit of the Attachment 1 of Appendix 2 of the Manufacturing site EA for the the first page states that "sewage disposed of at sea by However, the fourth page of the audit states that "sludge will be incinerated and not disposed of at sea before the year 2000." Please clarify how the waste from this facility will be disposed of.

D. Please provide updated information regarding the permit status of the which is used to dispose of any Zofran Oral Solution that is returned in the United States. The facility has been operating under an expired permit since 1991

IV. METHODS VALIDATION

A. According to the FDA Guideline for Methods Validation, the list submitted with the application should show, among other things, package size and type of the samples to be submitted. The list submitted documents several materials which are submitted in vials; however, it does not include the size or volume of one vial of material. Please confirm this size or volume for each material.

B. A specific reference to approved NDA 20-007, including volume page number should be provided for the following sections: drug substance specifications; information needed to support the integrity of the reference standard; analytical methods for the drug substance; validation of the analytical methods for the drug substance.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/RFrankewich
HFD-820/Yuan Yuan Chiu (only for CMC related issues) SBF 5/14/96

drafted: kj/May 13, 1996/c:\wpfiles\cso\n\20605605.0kj
r/d Initials: JGibbs 5/15/96
Sfredd 5/15/96

INFORMATION REQUEST (IR)

Johnson

NDA 20-605

AUG - 5 1996

AUG - 5 1996

GlaxoWellcome Inc.
Attention: John West
Five Moore Drive, P.O. Box 13358
Research Triangle Park, NC 27709

Dear Mr. West:

We acknowledge receipt on July 27, 1996 of your July 25, 1996 amendment to your supplemental new drug application for Zofran (ondansetron hydrochloride) Oral Solution.

This amendment contains additional chemistry, manufacturing and controls information submitted in response to our May 24, 1996 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.

The due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is January 27, 1997.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

8/2/96

8/5/96

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-180/K.Johnson
DISTRICT OFFICE
HFD-180/RFrankewich

drafted: kj/August 2, 1996/c:\wpfiles\cso\n\20605608.0kj
REVIEW EXTENSION

Johnson

NDA 20-605

OCT - 8 1996

Glaxo Wellcome Inc.
Attention: John West
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. West:

Please refer to your pending June 22, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron HCl) Oral Solution.

We also refer to your amendment dated August 28, 1996 containing final printed labeling submitted in response to our May 31, 1995 approvable letter.

We have completed our review of the labeling and find it acceptable.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

KJ 10/7/96

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-605
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
drafted: kj/October 7, 1996/c:\wpfiles\cso\n\20605610.1kj

INFORMATION REQUEST (IR)

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-605

Name of Drug: Zofran (ondansetron) Oral Solution

OCT - 8 1996

Sponsor: Glaxo Wellcome Inc.

Material Reviewed

Submission Date(s): August 28, 1996

Receipt Date(s): August 29, 1996

Background and Summary Description: This NDA was submitted June 22, 1996 to market an oral solution as an alternate dosage form to the 4 and 8 mg tablet formulations (NDA 20-103), approved December 31, 1992. NDA 20-605 was approvable on May 31, 1996 pending an adequate response to our May 23, 1996 letter requesting additional chemistry information, and final printed labeling. The firm submitted a response to the chemistry information request letter on July 27, 1996, which is currently under review.

Review

The final printed labeling (August 1996, RL-339) was compared to that which accompanied the AE letter. While the draft labeling states that the solution is marketed as a 60 ml bottle, the final printed labeling states that it is available as 50 ml. In a October 1, 1996 telephone conversation with Mr. John West, Glaxo Wellcome Regulatory Affairs, he clarified that it will be marketed as a 50 mg solution in a 60 ml bottle.

The package insert also contains the revisions approved in NDA 20-1-3/S-011 (modification of the OVERDOSAGE section to state, "Hypotension (and faintness) occurred in a patient that took 48 mg of oral ondansetron, The events resolved completely.") Other than the modifications noted above, the labeling was identical as that upon which the AE letter was based, with only minor editorial revisions that were included in the cover letter.

The FPL submitted for the cartons and bottle labels are identical to that which was AE on May 31, 1996.