CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020951

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

D.F.

SEP 14 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-951
Cimetidine Oral Suspension, 200 mg/20 ml
Tagamet HB® 200 Suspension

Sponsor: SmithKline Beecham Consumer Healthcare

Reviewer: Carol Cronenberger, Ph.D.

Submission Date: December 29, 1997

Type of Submission: New OTC Formulation

Synopsis:

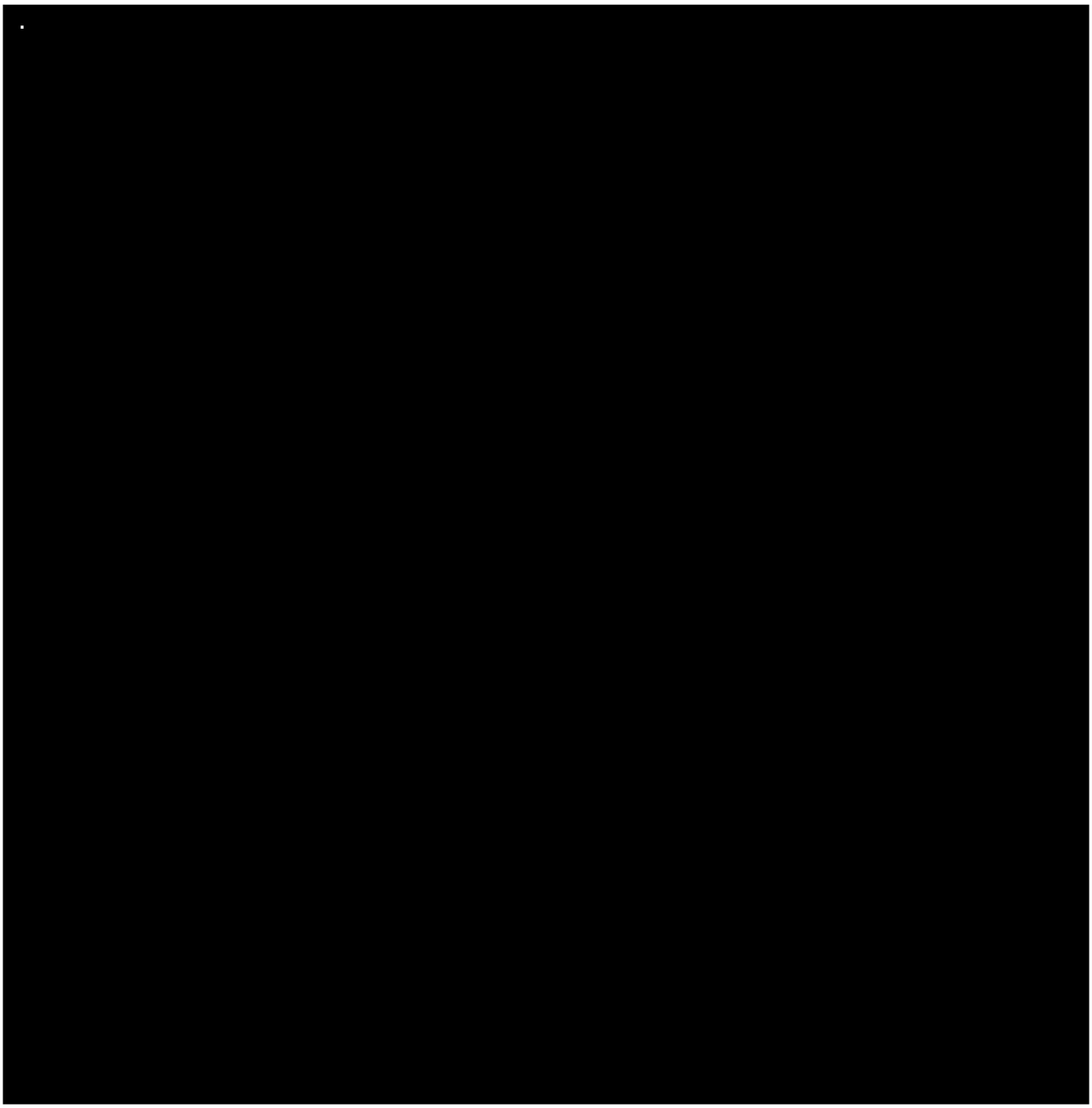
Cimetidine is a histamine-2 (H_2) receptor antagonist that inhibits all phases of gastric secretion through its effect on the gastric parietal cell. The purpose of the current submission is to obtain approval for a new dosage form (oral suspension) for nonprescription cimetidine. The tablet formulation is the only dosage form currently approved for nonprescription cimetidine (Tagamet HB® 200) and is indicated for the relief and prevention of heartburn, acid indigestion, and sour stomach. The suspension product contains 200 mg of cimetidine per 20 mL and would be indicated for the same approved uses as the tablet. The dose is 4 teaspoons or 20 mL (200 mg) and can be taken up to twice a day. According to the sponsor, this new dosage form has been developed for consumers who have difficulty swallowing tablets or who prefer a liquid form.

The Human Pharmacokinetic and Bioavailability Section contains one bioequivalence (BE) study (#143-09-11255) comparing the oral bioavailability of cimetidine after a 200 mg dose of the proposed suspension to the bioavailability of the 200 mg OTC tablet. Under fasting conditions the sponsor has demonstrated equivalence in the extent of absorption (AUC) between the two dosage forms, but mean peak plasma concentrations (C_{max}) for cimetidine were slightly outside the acceptable statistical equivalence criteria. Lastly, the new oral suspension reached C_{max} about 0.6 hours sooner than the marketed OTC tablet. These minor changes in pharmacokinetics are not expected to result in significant pharmacodynamic differences and are not considered to be clinically relevant.

The sponsor is requesting approval of the current NDA based solely on the BE study (i.e., no new clinical safety/efficacy trials have been performed). The suspension formulation used in the BE study was the to-be-marketed formulation and was manufactured from a representative production-scale size batch; i.e., >10% of production scale. The new cimetidine drug substance (cimetidine polymorph B) and final formulation were made at the manufacturing sites that will be used to make the approved drug product (i.e., drug substance at SmithKline Beecham

[redacted]

The sponsor claims that because the new cimetidine product is a suspension, requirements for dissolution data are not applicable. However, the Agency has required dissolution methods and specifications for suspension formulations of other drugs in the past and it is currently considering developing a guidance for industry which will address the dissolution of suspensions, solutions, and suppositories. Therefore, the sponsor should be informed of this for consideration of developing a dissolution method and specification for the new cimetidine suspension.



Comments (to be sent to firm):

1. A food effect bioavailability study comparing OTC cimetidine tablets and the new oral suspension should be conducted in accordance with the "Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies", FDA, CDER, October, 1997. This draft guidance can be located on the Internet at http://www.fda.gov/cder/guidance/index.htm. Before the study is initiated, the protocol should be submitted to the Agency for review and comment.

2. Please develop an in vitro dissolution method and specification for the new cimetidine suspension. The Agency intends, at some time in the future, to develop a guidance for oral suspension products.

3. A commitment should be made to perform a pharmacokinetic/pharmacodynamic/safety study in pediatric subjects <12 years of age, if such data are not available. This suggestion is based on the following rationale:

a. data provided by the National Disease and Therapeutic Index (NDTI) of IMS America, indicates that [redacted] of the frequency of use for the currently marketed prescription Tagamet Liquid (solution) in a three-year period, from 1995 through 1997, was for individuals <13 years of age, primarily infants.

b. the pharmacokinetics of cimetidine are unknown in the pediatric population and may be substantially different than those observed in adults.

c. potential drug-drug interactions involving cimetidine in the pediatric population may not be reliably predicted from adult data.

RECOMMENDATION:

Although, under fasting conditions cimetidine Oral Suspension, 200 mg/20 ml, was equivalent to one 200 mg cimetidine Tiltab® Tablet (Tagamet HB® 200) according to the Two One-sided Tests Procedure and 90% confidence interval range of 80 to 125% using log transformed data for AUC_{0-T} and $AUC_{0-\infty}$, the equivalence criteria were not strictly met for C_{max}, which occurred about

30 minutes sooner for the suspension product. Review of previously submitted pharmacokinetic data for the same dose (200 mg) of the **approved** intravenous injection cimetidine product (NDA 17-939 submission dated 1/25/87) indicate that Cmax values obtained after administration of the cimetidine suspension product are only approximately 40-50% of those achieved at 15 minutes post-intravenous dose. In addition, the reviewing Medical Officer and the Medical Team Leader have stated in an HFD-180 Team Meeting held 8/25/98, that the differences observed between the tablet and suspension for the C_{max} and T_{max} data are not clinically important from a safety and efficacy perspective [see Comment #2 under "Comments (not to be sent to firm)"]. Overall, the information/data submitted under section 6 of the NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of the Pharmaceutical Evaluation II (DPEII).

OCPB/DPEII is also of the opinion that:

1) A Food Effect study is needed for the new oral suspension since there is no food effect information on any of the SmithKline Beecham approved oral cimetidine dosage forms [redacted] Therefore, Comment #1 under "Comments (to be sent to the firm)" should be communicated to the firm. This study could be done post-NDA approval unless the Medical Officer feels that the information is needed prior to approval from a safety and/or efficacy perspective.

2) Comment #2 under "Comments (to be sent to the firm)" regarding dissolution should also be communicated to the firm.

3) Since the new oral suspension could potentially be used in pediatric subjects <12 years of age, there is a need for pharmacokinetic/pharmacodynamic/safety information for this population.

Carol Cronenberger, Ph.D.
Division of Pharmaceutical Evaluation II
/S/ [redacted] 9/14/98

FT initialed by J. Hunt
/S/ [redacted] 9/13/98
Interim Team Leader,
Gastrointestinal and Coagulation Drug Products

cc: NDA 20-951, HFD-345 (Subramaniam), HFD-180 (Division Files), HFD-850 (Lesko), HFD-870 (Chen, Hunt), Central Document Room (Barbara Murphy). Biopharm Briefing held 9/2/98 (Chen, Hunt, Lee, Choi, Kavanaugh in attendance).

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Background:

The original NDA for nonprescription cimetidine tablets was submitted to the FDA in August of 1992. At that time, the firm had not undertaken any drug interaction studies, therefore, the Biopharmaceutics Reviewer (Dr. Patrick Marroum) recommended non-approval of cimetidine for OTC use due to concern for potential drug interaction possibilities. OTC cimetidine was the subject of two combined GI and OTC Drug Advisory Committee Meetings in September 1993 and July 1994 for efficacy and risk-benefit assessment, respectively. Subsequently, the firm submitted the results of two drug interaction studies performed in healthy adults with OTC cimetidine and theophylline and triazolam. The data revealed significant increases in triazolam AUC_{inf} (25-30%) when coadministered with cimetidine 200 mg bid for 1 to 8 days, with a small number of subjects showing increases in this parameter of 50 to 150%. A similar study with theophylline failed to reveal any consistent drug interaction. The reviewing Medical Officer (Dr. Robie-Suh) recommended non-approval of OTC cimetidine in a memo dated March 21, 1995. However, after strong recommendation from the combined OTC and GI Advisory Committee, which met again on March 27, 1995, Dr. Robie-Suh withdrew non-approval on April 14, 1995 provided the labeling contained a prominent warning regarding possible drug interaction potential between cimetidine and some prescription medications. The NDA submission was approved on June 16, 1995. In the current submission, the sponsor is seeking approval for an OTC suspension formulation of cimetidine. It should be noted that this drug has not been previously approved for prescription purposes as a suspension formulation (available as tablets, oral solution, and injection).

The potential for use of the cimetidine OTC suspension product in pediatric subjects was discussed in a Team Progress Meeting held between members of HFD-180 and OTC on June 15, 1998. The current labeling does not recommend OTC tablets for children <12 years old or use of prescription cimetidine products in individuals <16 years of age. However, according to data provided by the National Disease and Therapeutic Index (NDTI) of IMS America, [redacted] of the frequency of use for the currently marketed prescription Tagamet Liquid (solution) in a three-year period, from 1995 through 1997, was for individuals <13 years of age, primarily infants. This is of particular concern as the pharmacokinetic, efficacy, and safety database for the pediatric population (<16 years) is sparse. As many of the physiological functions governing drug absorption, distribution, and elimination in this population are either altered or not yet fully developed, especially during the first few months of life, collection of the appropriate data for the various pediatric subgroups is crucial to the establishment of appropriate dosage regimens and safety profiles.

Chemistry/Formulation:

Cimetidine has been manufactured to date as [redacted] This [redacted] form is used in the manufacture of the oral dose formulations (tablets and solution) plus injection for the prescription and OTC products. Cimetidine [redacted] is used in the manufacture of the proposed OTC suspension dosage form, and was selected as the active ingredient rather than

[redacted] due to its [redacted]
Cimetidine [redacted] will eventually convert to cimetidine [redacted] in an aqueous suspension over time. However, such [redacted] transition leads to the formation of small clusters of cimetidine [redacted] resulting in a suspension of inferior quality.

The cimetidine suspension product used in the BE study was obtained from a batch size of [redacted] kg, which is [redacted] production scale [redacted], and was identical to the intended to-be-marketed formulation. The quantitative formulations for the cimetidine suspension and the OTC tablets used in the BE study are listed below:

Quantitative formulation of cimetidine suspension (200 mg/20 ml)

Ingredient Name	%w/w	mg/dose (20 ml)	Function
Purified Water [redacted]	[redacted]	[redacted]	[redacted]
Cimetidine [redacted]			
Microcrystalline Cellulose/ Carboxymethylcellulose Sodium, [redacted]			
Saccharin Sodium, [redacted]			
Propylene Glycol, [redacted]			
Propylparaben [redacted]			
[redacted]			
Xanthan Gum [redacted]			
FD&C Blue #1 [redacted]			
Sucrose [redacted]			
[redacted]			

[redacted]

Dissolution

No dissolution data for cimetidine suspension was provided by the sponsor.

Bioavailability of the cimetidine suspension:

An open-label, randomized, two-way crossover study was conducted in 24 healthy males and females under fasting conditions to investigate the BE of cimetidine suspension (200 mg/20 ml) to cimetidine nonprescription tablets (200 mg). There was a 7-day washout period between treatments. Plasma samples were collected and assayed for cimetidine using a validated HPLC method. The following table summarizes the PK parameters and bioequivalence analysis:

PK parameter	Mean (SD)		Geometric mean ratio (Test/Reference)	90% Confidence Interval
	Test[a]	Reference[b]		
AUC_{0-T} (μg*hr/ml)	1.474 (0.018)	1.476 (0.018)	1.00	0.96, 1.04
$AUC_{0-\infty}$ (μg*hr/ml)	1.563 (0.018)	1.560 (0.018)	1.00	0.96,1.05
C_{max} (μg/ml)	0.325 (0.035)	0.182 (0.035)	1.15	1.06,1.26
T_{max} (hr)[c]	1.006 (0.147)	1.622 (0.147)	0.62	

[a]Cimetidine suspension, 200 mg/20 ml.
[b]Cimetidine tablets, 200 mg.
[c]Values represent arithmetic means and ratio.

Based on the logarithmic transformation, the 90% confidence intervals about the ratios of test/reference means for AUC_{0-T} and $AUC_{2-\infty}$ were within the .80 - 1.25 limit when the oral suspension product was compared to the tablet product. The 90% confidence interval observed for C_{max} was 1.06,1.26. This reviewer also analyzed the data using SAS with PROC GLM for ANOVA and the Two One-sided Tests Procedure and concurs with the results submitted by the sponsor. Technically, 200 mg/20 ml cimetidine Oral Suspension is not equivalent to one 200 mg cimetidine Tiltab® Tablet (Tagamet HB® 200), as the C_{max} data exceeded the established criteria.

The oral suspension product exhibited slightly higher mean (±SD) C_{max} (1.44±0.05 vs 1.25±0.05 μg/ml), and earlier mean (±SD) T_{max} (1.01±0.15 vs 1.62±0.15 hr) values than the reference tablet product. Furthermore, these trends were noted for the vast majority of individual subjects as well, with some subjects exhibiting 2-3 times greater C_{max} values after administration of the suspension when compared to the tablet. These observations are not surprising in view of the differences in formulation (tablets are expected to show slower absorption due to additional time required for tablet disintegration). Although the extent of absorption was very similar between the cimetidine tablet and suspension, significant differences existed in the rate of absorption between the two products. The Medical Officer will be asked to comment on the clinical relevance of these observations from a safety and efficacy perspective. There were no serious or unexpected adverse events and both products appeared to be equally well tolerated.

Title: BIOAVAILABILITY OF CIMETIDINE ORAL SUSPENSION (200 MG/20 ML) VERSUS TAGAMET HB® 200 TABLETS

Study No. 143-09-11255

OBJECTIVE:

The objective of this relative bioavailability study was to compare the oral bioavailability of cimetidine after a 200 mg dose of the test oral suspension formulation with the oral bioavailability of cimetidine after a 200 mg dose of the marketed cimetidine 200 mg Tiltab® tablet (Tagamet HB® 200), when administered to adult volunteers, under fasted conditions.

Study Site and Investigator:

The study was conducted at the clinical facility of:

[redacted]

The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 12 hours after drug administration for each treatment period.

Clinical Study Dates:

Period I confinement for all subjects began June 24, 1997 and ended June 25, 1997. Drug was administered June 25, 1997.

Period II confinement for all subjects began July 1, 1997 and ended July 2, 1997. Drug was administered July 2, 1997.

METHODS:

Study Design:

The protocol was designed as an open label, randomized, single oral dose, two-treatment, two-period crossover with a period of seven days separating drug administrations. Twenty-six healthy male and female subjects were enrolled in the study after being screened from the general population.

Subject Eligibility:

Medical history, physical examination (including vital signs), and diagnostic laboratory results, obtained within 30 days of the study start, were reviewed and approved by the investigating physicians for all subjects. Subject demographic data are presented in Table 1 (see Appendix). Fourteen female and 12 male subjects were enrolled in the study. The average age of the subjects

was 35 years of age. The average height and weight of the subjects was 68 inches and 151.6 pounds, respectively. There were no clinically significant prestudy laboratory findings. All results fell within acceptable limits.

Drug Administration:
A single dose of cimetidine oral suspension (200 mg/20 mL) or one 200 mg tablet was administered with 240 mL of water according to a randomization schedule for each period. The subjects were dosed at two minute intervals starting at 0800 hours. Subjects were dosed at the same time for both periods of the study. The subjects were not allowed to be supine for 4 hours after dosing, and were not permitted to smoke from 1 hour prior to dosing until 4 hours postdose or within one hour prior to scheduled blood pressure measurements, each period.

Foods and Fluids:
The subjects fasted for 10 hours prior to and 5 hours after drug administration. A standardized menu was served to all study subjects throughout the in-house portion of the study. Water was allowed *ad lib* except within one hour of dosing, when only the water for dosing was allowed.

Products Studied:
Test Product = Cimetidine Oral Suspension, 200 mg/20 mL
Manufactured by: SmithKline Beecham Consumer Healthcare
Lot #LDBZ-1
Formula: #3027101-0028
Batch size: 5400 kg
Expiration date: July 1997
This is the intended to-be-marketed formulation.

Reference Product = Cimetidine Tiltab® Tablets 200 mg (Tagamet HB® 200)
Manufactured by: SmithKline Beecham Consumer Healthcare
Lot #7D07C045
Formula: PR-3
Expiration date: March 31, 1999

Blood Sample Collection and Processing:
Ten mls of venous blood were obtained in Vacutainers with no anticoagulant for analysis of cimetidine at: 0 (prior to dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hours for both treatment periods. An additional ten mls of venous blood was obtained at predose (0 hour) of each period. The samples were centrifuged at 2500 rpm for approximately 30 minutes at 10°C. The serum was transferred to labeled polypropylene tubes and frozen at -20°C to await analysis.

Pharmacokinetic Analysis:
The serum levels of cimetidine were monitored for 12 hours after drug administration. They were used to calculate the area under the concentration-time curve (AUC) by linear interpolation between consecutive serum drug levels. AUC_{0-T} was calculated from zero to the last non-zero concentration (Cp_{last}). $AUC_{0-\infty}$ was calculated by extrapolation of AUC_{0-T} by Cp_{last}/Ke. The elimination rate constant (Ke) was estimated by linear least squares fitting of the logarithms of the last four to five concentrations versus time. Half-life ($t_{\frac{1}{2}}=\ln 2/Ke$), C_{max}, T_{max}, first peak concentration (C_{max1}), time to first peak (T_{max1}), and $C_{max}/AUC_{0-\infty}$ were also reported.

The arithmetic mean and standard deviation were calculated for each pharmacokinetic parameter and for the cimetidine concentration at each time point. The geometric means were calculated for AUC_{0-T}, $AUC_{0-\infty}$, C_{max}, and $C_{max}/AUC_{0-\infty}$.

Statistical Analysis:
The statistical analyses (report attached) were performed at [redacted] using SAS® version 6.11 and PROC GLM for the Analysis of Variance (ANOVA). All parameters were analyzed by ANOVA and the F-test to determine statistically significant (=0.05) differences between the drug formulations.

All parameters, including the logarithmic transformations of AUC, C_{max}, C_{max1}, and $C_{max}/AUC_{0-\infty}$ were analyzed by ANOVA using type III sum of squares to determine statistically significant differences (=0.05). The least squares means were computed using the general linear model with effects for sequence, subject nested within sequence, period and drug.

The power of the study to detect a 20% difference in parameter means as statistically significant (=0.05) was calculated using the sample estimates and significance level of the central Student's t-distribution.

The intrasubject percent coefficient of variation (%CV) was reported for each parameter. For the untransformed parameters, %CV=100xSqrt(MSE)/(grand mean), and for the log transformed parameters, %CV=100xSqrt (exp(MSE)-1), where MSE is the mean squared error from the ANOVA, and the grand mean is the mean of all of the observations used in the ANOVA.

There was no significant period effect (=0.05) or sequence effect (=0.10) for any analysis of AUC or CMAX. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

Analytical Methods and Validation:
[redacted]

[redacted]

a. Sample Receipt and Storage

Serum samples were transferred from the clinic to the laboratory on July 7, 1997. All samples were stored in the laboratory -20°C freezer until the completion of the analytical portion of the study.

b. Sample Analysis

Sample analysis began on July 8, 1997 and was completed on July 18, 1997.

c. Analytical Reference Standards

Reference standard cimetidine (USP Lot H) was used to prepare serum calibration standards and control samples. Sigma reference standard n-propionylprocainamide (Lot 124H3692) was used as internal standard. Reference standards were used as received.

d. Linearity

For analytical runs in which the QC criteria for acceptance were met, the coefficients of determination of the calibration lines were greater than 0.996 for cimetidine. The weighting factor of [1/concentration squared] was used for least-squares linear regression analysis of all study data.

e. Accuracy

The accuracy of the assay for cimetidine was between 98.3 and 103% for all standard and control samples. Within-run accuracy was established during the method validation experiments and was found to be 93.1 to 97.3%.

f. Precision

The inter-run precision of the calibration standards was 0.744 to 2.81% for cimetidine. The inter-run precision of the control samples was 2.66 to 4.83% for cimetidine. Within-run precision of this assay was determined during validation and was found to be 3.55 to 7.51%.

g. Sensitivity and Range

The lower limit of quantitation (LLOQ) for the assay was 0.100 μg/mL for cimetidine during validation. The range of calibration for this assay was between 0.100 and 10.0 μg/mL. Serum sample values quantitating below 0.100 μg/mL were reported as zero.

h. Selectivity

The serum used to prepare calibration standards and control samples was screened chromatographically to confirm the absence of endogenous compounds that would interfere with the analysis of cimetidine. Selectivity was also confirmed by assaying a predose serum sample from each study phase for all subjects with and without the addition of internal standard.

i. Acceptance Criteria

In this study, calibration lines and duplicate control samples containing 6.00, 2.00 and 0.200 μg/mL cimetidine were analyzed with each sample set. The final assay results for each sample set were accepted only if a minimum of 4 out of 6 control samples processed with each sample set were within 15% of the nominal concentration for the 6.00 and 2.00 μg/mL control samples and 20% of the nominal concentration for the 0.200 μg/mL control samples. Also, one control sample at each concentration must have been within the specified range.

j. Stability

Serum samples spiked with known concentrations of cimetidine were prepared on June 24, 1997. The concentrations prepared were 6.00, and 0.200 μg/mL. Stability samples were stored with the study samples in the clinic -20°C freezer. Stability samples were transferred and stored with the study samples from the clinic -20°C freezer to the laboratory -20°C freezer on July 7, 1997. The stability samples were assayed during the course of study sample analysis. [redacted]

[redacted]

These data demonstrate the stability of cimetidine in serum for a 24-day period, which covered the duration of both the clinical and analytical portions of this study.

k. Analytical Notes

Subjects 5 and 11 did not complete the clinical portion of the study. Therefore, no analytical data was reported for these subjects.

RESULTS:

Subject Compliance and Protocol Deviations:

Twenty-six subjects who met the protocol inclusion/exclusion criteria were entered into the study. However, twenty-four subjects completed the study according to protocol, therefore, twenty-four sets of data were used in the analysis for cimetidine. Subject #5 was withdrawn from the study because a urine test for drugs of abuse was returned positive for cannabinoids at Period II check-in. Subject #11 did not return for Period II due to personal reasons. Blood samples were obtained with respect to dosing time for each subject. There were forty-one blood sampling time deviations.

Safety Monitoring:

Vital signs (blood pressure and pulse) were measured at 0 (predose), and at 4 and 12 hours postdose. Vital signs were recorded after at least three minutes in a sitting position. There were no clinically significant changes in vital signs measurements following drug administration. Diagnostic blood and urine specimens were obtained from the subjects at the 12 hour blood sample collection, Period II.

Adverse Events:

Two subjects reported experiencing an adverse event. Subject #17 reported feeling lightheaded approximately 4 hours after dosing (cimetidine suspension) in Period I and subject #19 reported a stomach ache 2.5 hours after dosing (cimetidine tablet) in Period II. Both of the events were judged as possibly drug related, were mild in intensity and resolved spontaneously within 2.5 hours of onset.

Pharmacokinetic Results:

The concentrations of cimetidine at each time point after each product are summarized in Table 2 (see Appendix). The mean concentrations after the suspension from 0.25 to 1.75 hours postdose were statistically significantly (=0.05) higher than the mean concentrations observed after the tablet. From 3 to 7 hours after dosing the mean concentrations after the suspension were significantly lower than after the tablet. By 10 hours after dosing cimetidine concentrations were less than 0.22 μg/ml for 42 of the 48 doses. The mean cimetidine concentration vs time profiles resulting from the two products were plotted on a rectilinear scale (Figure 1, Appendix) and on a semi-logarithmic scale (Figure 2, Appendix).

Some of the blood samples were obtained at times that deviated from the scheduled time. In each instance, the $AUC_{0\text{-}T}$ was calculated using the actual times to determine whether it would differ appreciably from the AUC calculated using the scheduled times. The differences in

calculated AUCs ranged from -0.35% to 0.33%. Since these effects were very small, the scheduled phlebotomy times were employed to calculate the AUCs for the statistical analysis.

The blood sampling schedule proved suitable for this bioequivalence study. More than 80% of $AUC_{0-\infty}$ was measured by AUC_{0-T} for all 48 estimates of $AUC_{0-\infty}$ obtained. The first postdose sample was not the maximum observed concentration for any subject.

The arithmetic mean and standard deviation for all parameters are listed in Table 3 and the least squares means are listed in Table 4 (see Appendix). There were statistically significant differences between the formulations for C_{max}, ln C_{max}, $C_{max}/AUC_{0-\infty}$, ln $C_{max}/AUC_{0-\infty}$, and T_{max}. Based on the least squares estimates of the geometric means, the AUC_{0-T} and $AUC_{0-\infty}$ for the test product were both within 1% of the respective estimates for the reference product. The C_{max} for the test product was 15% higher than the reference product and occurred 38% earlier (37 minutes). Furthermore, individual ratios revealed that 20/24 subjects had greater C_{max} values for the suspension product as compared to the tablets; thirteen of these subjects had C_{max} values which were up to 50% greater, three had values between 50 and 100% greater, and four had values which were 2-3 times as high (Table 5, Appendix). Likewise, 15/24 subjects had T_{max} values which were shorter for the suspension than the tablets (Table 6, Appendix).

The results of the statistical analysis of the cimetidine PK data are displayed in the table below. Based on the logarithmic transformation, the 90% confidence intervals about the ratios of test/reference means for AUC_{0-T} and $AUC_{0-\infty}$ were within the 0.80 - 1.25 limit when the oral suspension product was compared to the tablet product. The 90% confidence interval observed for C_{max} was 1.06,1.26. This reviewer also analyzed the data using SAS with PROC GLM for ANOVA and the Two One-sided Tests Procedure and concurs with the results submitted by the sponsor.

Statistical analysis of cimetidine PK data.

PK parameter	Mean (SD)		Geometric mean ratio (Test/Reference)	90% Confidence Interval
	Test[a]	Reference[b]		
AUC_{0-T} (µg*hr/ml)	1.474 (0.018)	1.476 (0.018)	1.00	0.96, 1.04
$AUC_{0-\infty}$ (µg*hr/ml)	1.563 (0.018)	1.560 (0.018)	1.00	0.96,1.05
C_{max} (µg/ml)	0.325 (0.035)	0.182 (0.035)	1.15	1.06,1.26
T_{max} (hr)[c]	1.006 (0.147)	1.622 (0.147)	0.62	

[a]Cimetidine suspension, 200 mg/20 ml.
[b]Cimetidine tablet, 200 mg.
[c]Values represent arithmetic means and ratio.

CONCLUSION:

Cimetidine Oral Suspension, 200 mg/20 ml, was equivalent to one 200 mg cimetidine Tiltab® Tablet (Tagamet HB® 200) according to the Two One-sided Tests Procedure and 90% confidence interval range of 80 to 125% using log transformed data for AUC_{0-T} and $AUC_{0-\infty}$. The C_{max} data did not meet the equivalence criteria as the upper range of the confidence interval was just outside the acceptable limits. As the test oral suspension product exhibited slightly higher mean C_{max} and earlier mean T_{max} values than the reference tablet product, the Medical Officer will be asked to comment on the clinical significance of these observations from a safety and efficacy perspective. There were no serious or unexpected adverse events and both products appeared to be equally well tolerated.

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APPENDIX

TABLE 1: DEMOGRAPHIC INFORMATION
CIMETIDINE ORAL SUSPENSION (200 MG/20 ML) VERSUS
TAGAMET HB® 200 TABLETS
#143-09-11255

Subject #	Initials	Date of Birth	Age	Race [1]	Gender [2]	Frame Size [3]	Height (in.)	Weight (lbs.)
1	[redacted]	07/21/51	45	B	F	M	65	109
2		03/11/68	29	B	F	S	68	127
3		08/31/49	47	C	M	M	68	163
4		05/24/47	50	B	M	M	67	172
5		07/04/55	41	B	F	M	69	167
6		11/22/56	40	C	F	M	62	121
7		03/27/63	34	B	M	S	69	130
8		08/24/62	34	B	M	M	74	192
9		04/14/78	19	B	F	S	65	124
10		06/17/77	20	B	F	M	69	151
11		12/01/57	39	C	M	M	70	146
12		10/15/52	44	C	M	M	71	181
13		11/30/74	22	B	F	L	67	172
14		08/17/53	43	C	F	M	64	149
15		11/27/50	46	B	M	S	78	179
16		08/30/60	36	B	M	M	74	188
17		12/23/61	35	B	F	M	64	118
18		08/08/54	42	C	F	M	61	108
19		12/11/72	24	B	F	M	64	118
20		01/21/66	31	B	M	M	75	180
21		10/15/75	21	C	F	M	62	130
22		12/14/67	29	B	F	M	65	158
23		02/13/75	22	C	M	M	69	152
24		03/10/63	34	B	F	M	67	146
25		04/25/54	43	C	M	L	70	181
26		02/13/57	40	B	M	M	70	180

(1) A=ASIAN, B=BLACK, C=CAUCASIAN, H=HISPANIC
(2) M=MALE, F=FEMALE
(3) S=SMALL, M=MEDIUM, L=LARGE

TABLE 2: CIMETIDINE SERUM CONCENTRATIONS (μg/mL)
ARITHMETIC MEANS ± STANDARD DEVIATION(N = 24)
#143-09-11255

Time (Hours)	Test: Oral Suspension N Mean ± Std. Dev.	Reference: Tiltab Tablets N Mean ± Std. Dev.	Ratio Test/Reference Mean	Significance
0	24 0.0000	24 0.0000	--	--
0.25	24 0.3472 ± 0.2749	24 0.0714 ± 0.1280	4.86	p<0.05
0.5	24 1.086 ± 0.5454	24 0.6763 ± 0.4164	1.61	p<0.05
0.75	24 1.315 ± 0.4781	24 1.001 ± 0.4606	1.31	p<0.05
1	24 1.205 ± 0.3354	24 0.9986 ± 0.3924	1.21	p<0.05
1.25	24 1.090 ± 0.2989	24 0.9218 ± 0.3139	1.18	p<0.05
1.5	24 1.070 ± 0.2973	24 0.8741 ± 0.2638	1.22	p<0.05
1.75	24 1.013 ± 0.2526	24 0.8598 ± 0.2154	1.18	p<0.05
2	24 0.9401 ± 0.2219	24 0.8885 ± 0.2414	1.06	N.S.
2.33	24 0.8568 ± 0.1822	24 0.9022 ± 0.2301	0.95	N.S.
2.67	24 0.7880 ± 0.1841	24 0.8716 ± 0.1860	0.90	N.S.
3	24 0.7269 ± 0.1650	24 0.8140 ± 0.1689	0.89	p<0.05
3.5	24 0.6068 ± 0.1704	24 0.7266 ± 0.2430	0.84	p<0.05
4	24 0.5164 ± 0.1372	24 0.6216 ± 0.2185	0.83	p<0.05
5	24 0.3641 ± 0.1070	24 0.4388 ± 0.1291	0.83	p<0.05
6	24 0.2521 ± 0.0734	24 0.3024 ± 0.1233	0.83	p<0.05
7	24 0.1801 ± 0.0702	24 0.2147 ± 0.0912	0.84	p<0.05
8	24 0.1210 ± 0.0580	24 0.1394 ± 0.0781	0.87	N.S.
10	24 0.0051 ± 0.0251	24 0.0285 ± 0.0600	0.18	p<0.05
12	24 0.0000 ± 0.0000	24 0.0000 ± 0.0000	--	--

TABLE 3: PHARMACOKINETIC PARAMETERS FOR SERUM CIMETIDINE
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 24)
#143-09-11255

Parameter	Test: Oral Suspension N Mean ± Std. Dev.	C.V.	Reference: Tiltab Tablets N Mean ± Std. Dev.	C.V.	Ratio Test/Reference Mean
AUC 0-T ($\mu g\ mL^{-1} hr$)	24 4.462 ± 0.8252	18.5	24 4.464 ± 0.9253	20.7	1.00
Ln AUC 0-T Geometric Mean	24 1.4788 ± 0.1885 4.388		24 1.4758 ± 0.2055 4.375		1.00
AUC 0-Inf ($\mu g\ mL^{-1} hr$)	24 4.860 ± 0.8357	17.2	24 4.851 ± 0.9644	19.9	1.00
Ln AUC 0-Inf Geometric Mean	24 1.5668 ± 0.1734 4.791		24 1.5609 ± 0.1950 4.763		1.01
Cmax ($\mu g/mL$)	24 1.436 ± 0.3963	27.6	24 1.241 ± 0.3474	28.0	1.16
Ln Cmax Geometric Mean	24 0.3248 ± 0.2787 1.384		24 0.1779 ± 0.2845 1.195		1.16
Tmax (hr)	24 1.007 ± 0.6225	61.8	24 1.643 ± 0.9483	57.7	0.61
Rate Constant (hr^{-1})	24 0.3406 ± 0.04007	11.8	24 0.3580 ± 0.05892	16.5	0.95
Half-Life (hr)	24 2.062 ± 0.2438	11.8	24 1.989 ± 0.3423	17.2	1.04
Cmax/ AUCinf (hr^{-1})	24 0.2962 ± 0.06871	23.2	24 0.2574 ± 0.06189	24.0	1.15
Ln (Cmax/AUCinf) Geometric Mean	24 -1.2420 ± 0.2308 0.2888		24 -1.3830 ± 0.2302 0.2508		1.15

TABLE 4: PHARMACOKINETIC PARAMETERS FOR SERUM CIMETIDINE
LEAST SQUARES MEANS ± STANDARD ERROR (N =24)
#143-09-11255

Parameter	Test Oral Suspension Mean ± Std. Error	Reference Tiltab Tablets Mean ± Std. Error	Ratio Test/Reference Mean	Significance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
AUC 0-T (μg mL^{-1}hr)	4.441 ± 0.08240	4.462 ± 0.08240	1.00	N.S.	>0.99	9.0	0.95; 1.04
Ln AUC 0-T (Antiln)	1.4742 ± 0.0184 (4.368)	1.4756 ± 0.0184 (4.374)	1.00	N.S.	>0.99	9.0	0.96; 1.04
AUC 0-Inf (μg mL^{-1}hr)	4.842 ± 0.08794	4.847 ± 0.08794	1.00	N.S.	>0.99	8.8	0.95; 1.04
Ln AUC 0-Inf (Antiln)	1.5630 ± 0.0178 (4.773)	1.5603 ± 0.0178 (4.760)	1.00	N.S.	>0.99	8.7	0.96; 1.05
Cmax (μg/mL)	1.436 ± 0.04569	1.246 ± 0.04569	1.15	p=0.0076	0.96	16.7	1.06; 1.24
Ln Cmax (Antiln)	0.3254 ± 0.0345 (1.385)	0.1817 ± 0.0345 (1.199)	1.15	p=0.0075	0.97	17.0	1.06; 1.26
Tmax (hr)	1.006 ± 0.1466	1.622 ± 0.1466	0.62	p=0.0071	<0.50	54.0	0.40; 0.84
Rate Constant (hr^{-1})	0.3402 ± 0.00727	0.3601 ± 0.00727	0.94	N.S.	>0.99	10.2	0.90; 0.99
Half-Life (hr)	2.065 ± 0.04154	1.977 ± 0.04154	1.04	N.S.	>0.99	10.0	0.99; 1.10
Cmax/ AUCinf (hr^{-1})	0.2976 ± 0.00843	0.2587 ± 0.00843	1.15	p=0.0036	0.98	14.9	1.07; 1.23
Ln (Cmax/AUCinf) (Antiln)	-1.2376 ± 0.0310 (0.2901)	-1.3786 ± 0.0310 (0.2519)	1.15	p=0.0040	0.99	15.2	1.07; 1.24
First Cmax	1.418 ± 0.05385	1.086 ± 0.05385	1.31	p=0.0002	0.78	21.1	1.19; 1.43
Ln First Cmax (Antiln)	0.3064 ± 0.0490 (1.358)	0.0053 ± 0.0490 (1.005)	1.35	p=0.0003	0.79	24.3	1.20; 1.52
First Tmax (hr)	0.8871 ± 0.05662	0.8689 ± 0.05662	1.02	N.S.	0.54	31.5	0.86; 1.18

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant (α=0.05), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

Table 5

[redacted]

Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose
Comparison of First Cmax For Test And Reference Products

Subject	Seq	Oral Suspension	Tiltab Tablets	Ratio	Ln(Ratio)	Difference
1	BA	[redacted]				
2	AB					
3	AB					
4	BA					
6	BA					
7	AB					
8	BA					
9	BA					
10	AB					
12	BA					
13	BA					
14	AB					
15	BA					
16	AB					
17	AB					
18	BA					
19	AB					
20	BA					
21	AB					
22	BA					
23	AB					
24	BA					
25	AB					
26	BA					
MEDIAN		1.320	1.030	1.282	0.2482	0.290
MEAN		1.418	1.079	1.441	0.3063	0.339
STD		0.419	0.429	0.555	0.3372	0.371
CV		29.529	39.730	38.487	110.0902	109.484

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Table 6

[redacted]

Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose
Comparison of Tmax (hr) For Test And Reference Products

Subject	Seq	Oral Suspension	Tiltab Tablets	Ratio	Difference
1	BA	[redacted]			
2	AB				
3	AB				
4	BA				
6	BA				
7	AB				
8	BA				
9	BA				
10	AB				
12	BA				
13	BA				
14	AB				
15	BA				
16	AB				
17	AB				
18	BA				
19	AB				
20	BA				
21	AB				
22	BA				
23	AB				
24	BA				
25	AB				
26	BA				
MEDIAN		0.750	1.250	0.708	-0.250
MEAN		1.007	1.643	0.774	-0.635
STD		0.623	0.948	~~0.327~~	1.019
CV		61.812	57.737	68.075	160.38

[redacted]

Figure 1: Mean Cimetidine Serum Levels
#143-09-11255
N = 24

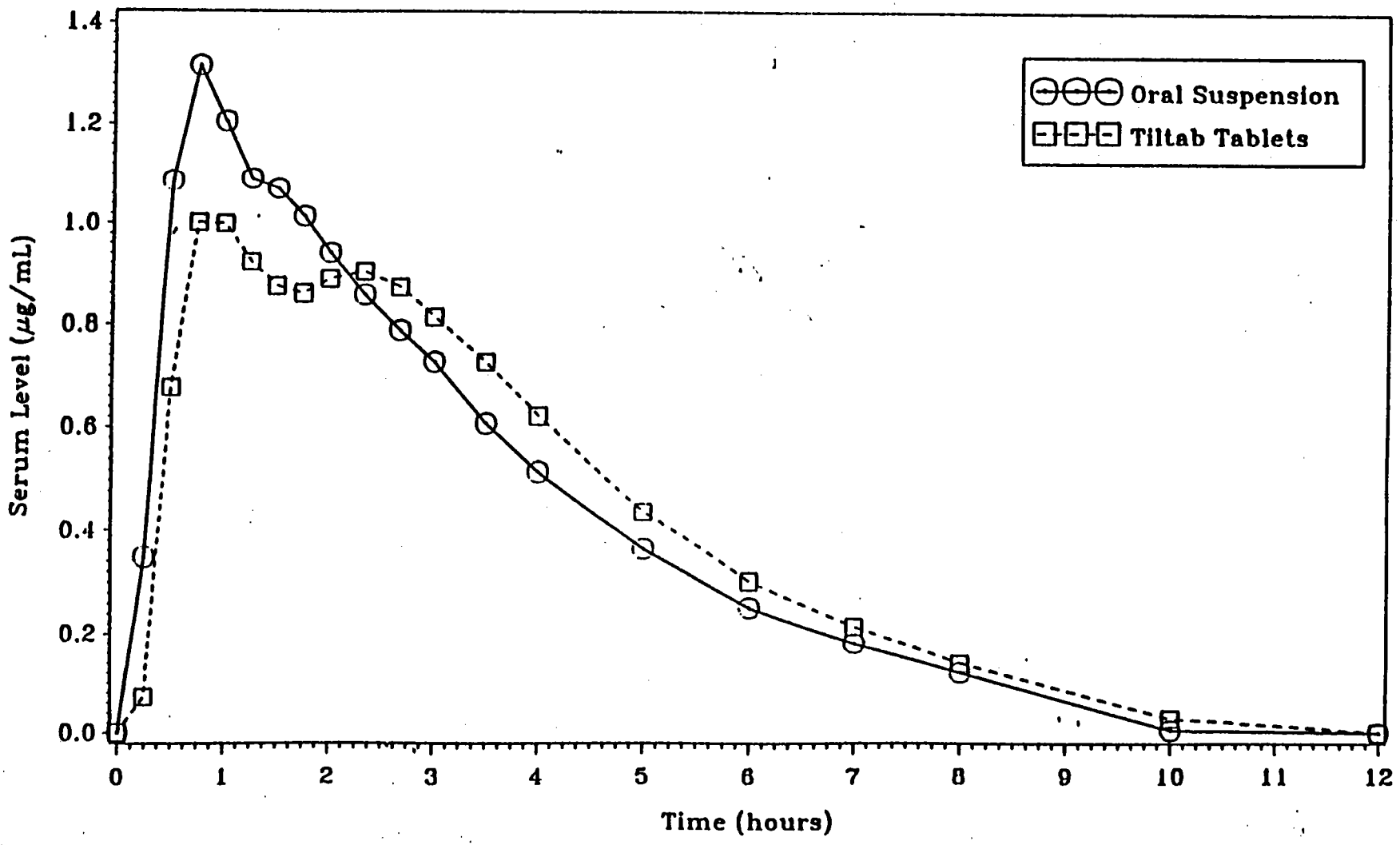
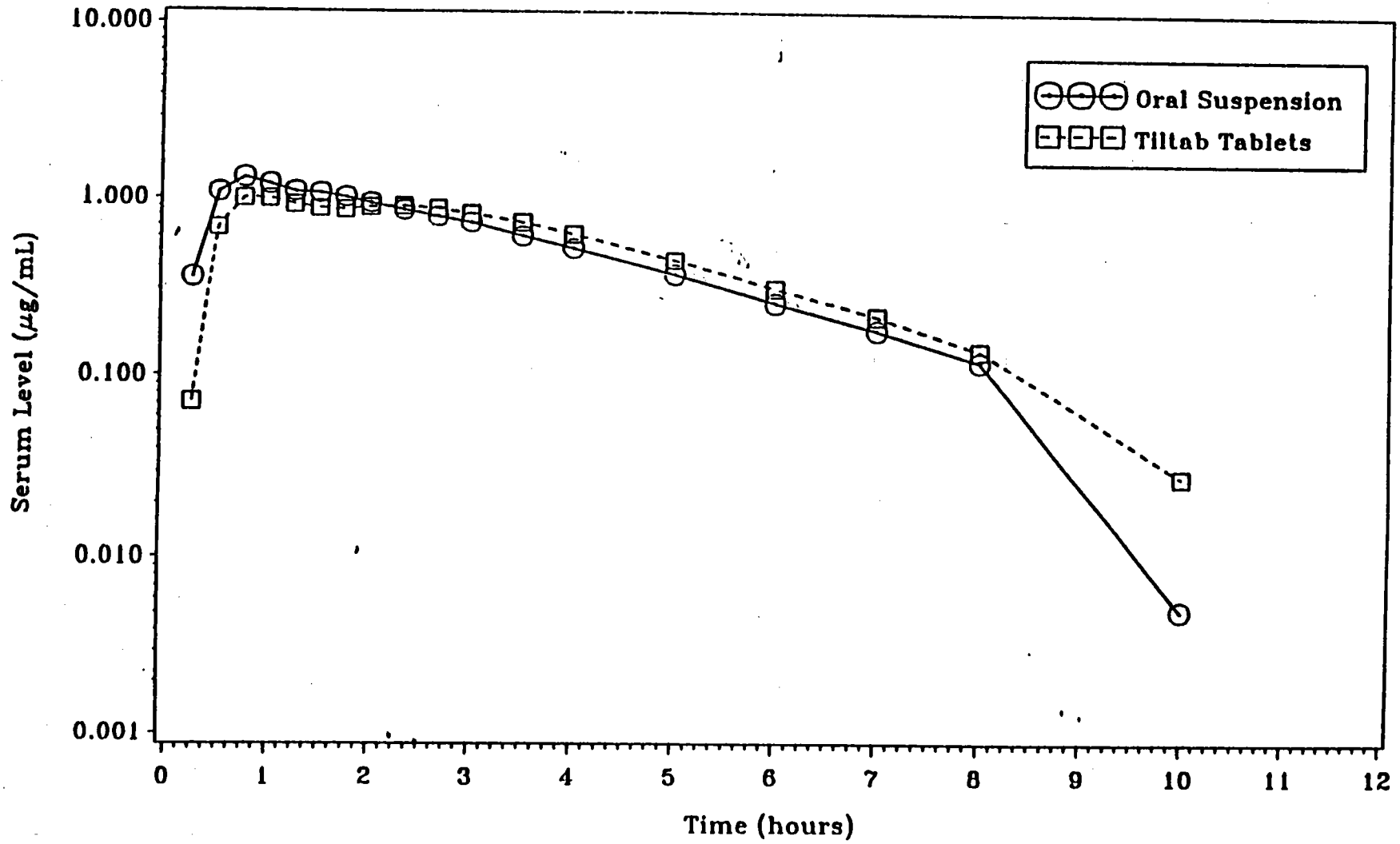


Figure 2: Mean Cimetidine Serum Levels (Semi-log Scale)
#113-09-11255
N = 24



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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SEQ	2	AB BA
SUBJECT	24	1 2 3 4 6 7 8 9 10 12 13 14 15 16 17 18 19 20 21 22 23 24 25 25
PERIOD	2	1 2
DRUG	2	Oral Suspension Tiltab Tablets

Number of observations in data set = 48

[redacted]

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: AUCT AUC 0-T (µg*hr/mL)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	31.79126312	1.27165052	7.86	0.0001
Error	22	3.56037336	0.16183515		
Corrected Total	47	35.35163648			

R-Square	C.V.	Root MSE	AUCT Mean
0.899287	9.014044	0.40228740	4.46289583

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.87208073	0.87208073	5.39	0.0299
SUBJECT(SEQ)	22	30.30560924	1.37752769	8.51	0.0001
PERIOD	1	0.60817519	0.60817519	3.76	0.0655
DRUG	1	0.00539796	0.00539796	0.03	0.8568

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.87208073	0.87208073	5.39	0.0299
SUBJECT(SEQ)	22	30.30560924	1.37752769	8.51	0.0001
PERIOD	1	0.61350546	0.61350546	3.79	0.0644
DRUG	1	0.00539796	0.00539796	0.03	0.8568

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.87208073	0.87208073	0.63	0.4347

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	-0.02128322	-0.18	0.8568	0.11653571
PERIOD 1 VS PERIOD 2	-0.22689860	-1.95	0.0644	0.11653571

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (μg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: LNAUCT Ln AUC 0-T

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	1.61108615	0.06444345	8.01	0.0001
Error	22	0.17701292	0.00804604		
Corrected Total	47	1.78809907			

R-Square	C.V.	Root MSE	LNAUCT Mean
0.901005	6.071855	0.08969973	1.47730370

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.03871817	0.03871817	4.81	0.0391
SUBJECT(SEQ)	22	1.53893413	0.06995155	8.69	0.0001
PERIOD	1	0.03341026	0.03341026	4.15	0.0538
DRUG	1	0.00002359	0.00002359	0.00	0.9573

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03871817	0.03871817	4.81	0.0391
SUBJECT(SEQ)	22	1.53893413	0.06995155	8.69	0.0001
PERIOD	1	0.03332585	0.03332585	4.14	0.0541
DRUG	1	0.00002359	0.00002359	0.00	0.9573

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03871817	0.03871817	0.55	0.4648

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	-0.00140694	-0.05	0.9573	0.02598446
PERIOD 1 VS PERIOD 2	-0.05288265	-2.04	0.0541	0.02598446

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: AUCI AUC 0-Inf (µg*hr/mL)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	33.40334151	1.33613366	7.25	0.0001
Error	22	4.05468897	0.18430404		
Corrected Total	47	37.45803048			

R-Square	C.V.	Root MSE	AUCI Mean
0.891754	8.841160	0.42930647	4.85577083

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.88579555	0.88579555	4.81	0.0392
SUBJECT(SEQ)	22	32.15997543	1.46181707	7.93	0.0001
PERIOD	1	0.35724752	0.35724752	1.94	0.1778
DRUG	1	0.00032301	0.00032301	0.00	0.9670

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.88579555	0.88579555	4.81	0.0392
SUBJECT(SEQ)	22	32.15997543	1.46181707	7.93	0.0001
PERIOD	1	0.35655301	0.35655301	1.93	0.1782
DRUG	1	0.00032301	0.00032301	0.00	0.9670

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.88579555	0.88579555	0.61	0.4446

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	-0.00520629	-0.04	0.9670	0.12436267
PERIOD 1 VS PERIOD 2	-0.17297552	-1.39	0.1782	0.12436267

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: LNAUCI Ln AUC 0-Inf

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	1.39992466	0.05599699	7.40	0.0001
Error	22	0.16656647	0.00757120		
Corrected Total	47	1.56649113			

R-Square	C.V.	Root MSE	LNAUCI Mean
0.893669	5.564021	0.08701266	1.56384493

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.03306004	0.03306004	4.37	0.0484
SUBJECT(SEQ)	22	1.34845146	0.06129325	8.10	0.0001
PERIOD	1	0.01832349	0.01832349	2.42	0.1341
DRUG	1	0.00008967	0.00008967	0.01	0.9143

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03306004	0.03306004	4.37	0.0484
SUBJECT(SEQ)	22	1.34845146	0.06129325	8.10	0.0001
PERIOD	1	0.01798397	0.01798397	2.38	0.1375
DRUG	1	0.00008967	0.00008967	0.01	0.9143

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03306004	0.03306004	0.54	0.4704

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	0.00274313	0.11	0.9143	0.02520607
PERIOD 1 VS PERIOD 2	-0.03884771	-1.54	0.1375	0.02520607

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (μg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: CMAX Cmax (μg/mL)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	5.74798496	0.22991940	4.62	0.0003
Error	22	1.09445871	0.04974812		
Corrected Total	47	6.84244367			

R-Square	C.V.	Root MSE	CMAX Mean
0.840049	16.66468	0.22304287	1.33841667

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.05274837	0.05274837	1.06	0.3143
SUBJECT(SEQ)	22	5.20271630	0.23648710	4.75	0.0003
PERIOD	1	0.06293008	0.06293008	1.26	0.2728
DRUG	1	0.42959021	0.42959021	8.64	0.0076

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.05274837	0.05274837	1.06	0.3143
SUBJECT(SEQ)	22	5.20271630	0.23648710	4.75	0.0003
PERIOD	1	0.03816821	0.03816821	0.77	0.3905
DRUG	1	0.42959021	0.42959021	8.64	0.0076

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.05274837	0.05274837	3.22	0.6414

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	0.18986713	2.94	0.0076	0.06461167
PERIOD 1 VS PERIOD 2	-0.05659441	-0.88	0.3905	0.06461167

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: LNCMAX Ln Cmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	3.28170187	0.13126807	4.61	0.0003
Error	22	0.62586659	0.02844848		
Corrected Total	47	3.90756846			

R-Square	C.V.	Root MSE	LNCMAX Mean
0.839832	67.10583	0.16866678	0.25134445

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.03338941	0.03338941	1.17	0.2904
SUBJECT(SEQ)	22	2.97237338	0.13510788	4.75	0.0003
PERIOD	1	0.02973632	0.02973632	1.05	0.3177
DRUG	1	0.24620277	0.24620277	8.65	0.0075

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03338941	0.03338941	1.17	0.2904
SUBJECT(SEQ)	22	2.97237338	0.13510788	4.75	0.0003
PERIOD	1	0.01702853	0.01702853	0.60	0.4474
DRUG	1	0.24620277	0.24620277	8.65	0.0075

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03338941	0.03338941	0.25	0.6240

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	0.14373716	2.94	0.0075	0.04885985
PERIOD 1 VS PERIOD 2	-0.03780168	-0.77	0.4474	0.04885985

[redacted]

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Cimetidine Oral Suspension (200 mg/20 mL) versus Tagamet HB 200 Tablets
PKL Protocol #11255; SKB Protocol MD-01010
Cimetidine Serum Levels (µg/mL) After Single 200 mg Dose

General Linear Models Procedure

Dependent Variable: TMAX Tmax (hr)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	23.17137764	0.92685511	1.81	0.0821
Error	22	11.27102028	0.51231910		
Corrected Total	47	34.44239792			

R-Square	C.V.	Root MSE	TMAX Mean
0.672757	54.02847	0.71576470	1.32479167

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.83023603	0.83023603	1.62	0.2163
SUBJECT(SEQ)	22	16.82421189	0.76473690	1.49	0.1773
PERIOD	1	1.00051875	1.00051875	1.95	0.1762
DRUG	1	4.51641097	4.51641097	8.82	0.0071

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.83023603	0.83023603	1.62	0.2163
SUBJECT(SEQ)	22	16.82421189	0.76473690	1.49	0.1773
PERIOD	1	0.67187764	0.67187764	1.31	0.2644
DRUG	1	4.51641097	4.51641097	8.82	0.0071

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.83023603	0.83023603	1.09	0.3088

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
TEST VS REFERENCE	-0.61562937	-2.97	0.0071	0.20734467
PERIOD 1 VS PERIOD 2	0.23744755	1.15	0.2644	0.20734467

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