Toxicology Research Laboratory

UIC The University of Illinois at Chicago

Department of Pharmacology (M/C 868)
1940 W. Taylor St.
Chicago, Illinois 60612-7353

20100915214

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified	3. DISTRIBUTION / AVAILABILITY OF REPORT Unlimited
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago 6b. OFFICE SYMBOL (*If applicable*)	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Materiel Development Activity
6c. ADDRESS (*City, State, and ZIP Code*) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353	7b. ADDRESS (*City, State, and ZIP Code*) ATTN: MCMR-RMA-RD Fort Detrick Frederick, MD 21702-5014
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity 8b. OFFICE SYMBOL (*If applicable*) MCMR-UMP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-92-C-2001
8c. ADDRESS (*City, State, and ZIP Code*) Fort Detrick Frederick, MD 21702-5009	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63807A; PROJECT NO. 30463807; TASK NO. QC; WORK UNIT ACCESSION NO. 073
11. TITLE (*Include Security Classification*) Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats	
12. PERSONAL AUTHOR(S) Levine, Barry S., Kirchner, Debra L. and Mercieca, Michael (PAI)	
13a. TYPE OF REPORT Study	13b. TIME COVERED FROM 7/3/95 TO _____
14. DATE OF REPORT (*Year, Month, Day*)	15. PAGE COUNT
16. SUPPLEMENTARY NOTATION	

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (*Continue on reverse if necessary and identify by block number*)
WR242511
Fertility
Early Embryonic Development

19. ABSTRACT (*Continue on reverse if necessary and identify by block number*)

This study evaluated the toxic potential of WR242511 Tartrate on reproductive capability in CD® male and female rats. WR242511 Tartrate is being developed as an anticyanide agent. Doses were based on a three month toxicity study in rats (UIC/TRL Study No. 107) in which mortality and toxicity was seen in males at doses of 4.5 mg/kg/day and on a developmental toxicity study in rats (UIC/TRL Study No. 144) in which maternal toxicity was observed at 8 mg/kg/day. In the present study, doses of 0, 0.3, 1.0, and 3.0 mg base/kg/day were administered by daily gavage to male rats for at least 60 days and to pregnant female rats for 23 - 27 days in sperm-positive animals and for 48 days in sperm-negative females. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. Lethality/toxicity was seen primarily in the high dose males; while only toxicity occurred in high dose females. Six of 25 high dose males were sacrificed moribund on day 15 or 21. Clinical signs in these and/or the remaining high dose animals included dark material around the nose, piloerection, hunched posture, and rough coat. Significant reductions in body weights, body weight gains, and food consumption occurred in males primarily at 3 mg base/kg/day. In males at 1 mg base/kg/day, sporadic, nonsignificant reductions in body weight gains contributed to a significant reduction in total body weight gains. Decreased organ weight/brain weight ratios were noted in high dose males for the epididymis, seminal vesicles, and prostate. However, there were no effects on sperm motility, count, or morphology in any group, and no apparent effects on the males' ability to impregnate the females. Females in the 3 mg base/kg/day group exhibited significantly reduced body weights and food consumption during the precohabitation and gestation periods. There were no effects on Cesarean section or estrous cycle parameters in any group. Both the mating and fertility indices were 100% in all WR242511 Tartrate groups. The no-observable-effect level (NOEL) for reproductive capability of males and females was 3 mg base/kg/day in spite of lethality and/or toxicity in both sexes at this dose level.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Barry S. Levine	22b. TELEPHONE (*Include Area Code*) (312) 996-5543 22c. OFFICE SYMBOL N/A

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-16
Study No.: 197

Title Page

Study Report for Task Order No. UIC-16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

Sponsor: U.S. Army Medical Materiel Development Activity

Test Article: WR242511 Tartrate

Contract No.: DAMD17-92-C-2001

Study Director

Debra L. Kirchner, Ph.D., D.A.B.T.

In-Life Phase Completed On

December 21, 1995

Performing Laboratory

TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, IL 60612-7353

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

STATEMENT OF COMPLIANCE

Study No. 197 entitled "Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Debra L. Kirchner, Ph.D., D.A.B.T. Date

DRAFT

QUALITY ASSURANCE STATEMENT

STUDY TITLE: ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

STUDY NUMBER: 197

STUDY DIRECTOR: DEBRA L. KIRCHNER

INITIATION DATE: 7/3/95

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 7/5/95, TO STUDY DIR 7/5/95, TO MGMT 7/5/95
PHASES: PROTOCOL REVIEW

INSPECT ON 10/30/95, TO STUDY DIR 10/30/95, TO MGMT 1/29/96
PHASES: ROOM ENVIRONMENT, VAGINAL WASHINGS AND MICRO-CHIP IDENTIFICATION IMPLANTATION

INSPECT ON 11/3/95, TO STUDY DIR 11/6/95, TO MGMT 11/21/95
PHASES: DOSING

INSPECT ON 11/17/95, TO STUDY DIR 11/20/95, TO MGMT 11/21/95
PHASES: RAT PAIRING

INSPECT ON 12/4/95, TO STUDY DIR 12/5/95, TO MGMT 12/7/95
PHASES: NECROPSY

INSPECT ON 3/26-27/96, TO STUDY DIR 3/27/96, TO MGMT 3/29/96
PHASES: DRAFT MALE REPRODUCTIVE ASSESSMENT REPORT

INSPECT ON 4/10-11/96, TO STUDY DIR 4/11/96, TO MGMT 4/15/96
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB

INSPECT ON 4/19-22/96, TO STUDY DIR 4/22/96, TO MGMT 4/29/96
PHASES: RAW DATA

INSPECT ON 4/24-25/96, TO STUDY DIR 4/25/96, TO MGMT 4/29/96
PHASES: DRAFT REPORT

Ronald Lehnenkeck 4/29/96

QUALITY ASSURANCE DATE

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-16
Study No.: 197

Signature Page

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

TRL Chemical No.: 1720614

Sponsor: U.S. Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Test Article: WR242511 Tartrate

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology (M/C 868)
1940 W. Taylor St.
Chicago, IL 60612-7353

_____ _____
Debra L. Kirchner, Ph.D., D.A.B.T. Date
Study Director

_____ _____
Barry S. Levine, D.Sc., D.A.B.T. Date
Principal Investigator

Study Initiation: July 3, 1995

Dosing Initiation: October 20, 1995

In-Life Completion: December 21, 1995

TABLE OF CONTENTS

TABLES

APPENDICES

1. SUMMARY

This study evaluated the toxic potential of WR242511 Tartrate on reproductive capability in CD® male and female rats. WR242511 Tartrate is being developed as an anticyanide agent. Doses were 0, 0.3, 1.0, and 3.0 mg base/kg/day and were based on a three month toxicity study in male and female rats (UIC/TRL Study No. 107) in which mortality and toxicity was seen in males at doses of 4.5 mg/kg/day and on a developmental toxicity study in female rats (UIC/TRL Study No. 144) in which maternal toxicity was observed at 8 mg/kg/day.

In the present study, doses of 0, 0.3, 1.0, and 3.0 mg base/kg/day were administered by daily gavage to male CD® rats for at least 60 days and to pregnant female CD® rats for 23 - 27 days in sperm-positive animals and for 48 days in sperm-negative females. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. The results are summarized in Table 1. Lethality/toxicity was seen primarily in the high dose males; while only toxicity occurred in high dose females. Six of 25 high dose males were sacrificed moribund on day 15 or 21. Clinical signs in these and/or the remaining high dose animals included dark material around the nose, piloerection, hunched posture, and rough coat. Significant reductions in body weights, body weight gains, and food consumption occurred in males primarily at 3 mg base/kg/day. In males at 1 mg base/kg/day, sporadic, nonsignificant reductions in body weight gains contributed to a significant reduction in total body weight gains in this group. Decreased organ weight to brain weight ratios were noted in high dose males for the epididymis, seminal vesicles, and prostate. However, there were no effects on sperm motility, count, or morphology in any group, and no apparent effects on the males' ability to impregnate the females. Females in the 3 mg base/kg/day group exhibited significantly reduced body weights and food consumption during the precohabitation and gestation periods. There were no effects on Cesarean section or estrous cycle parameters in any group. Both the mating and fertility indices were 100% in all WR242511 Tartrate groups. The no-observable-effect level (NOEL) for reproductive capability of males and females was 3 mg base/kg/day in spite of lethality and/or toxicity noted in both sexes at this dose level.

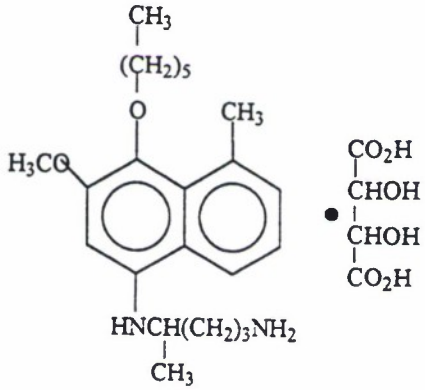
2. INTRODUCTION

This study was conducted to evaluate the toxic potential of WR242511 Tartrate on the reproductive capability of male and female rats. WR242511 Tartrate is being developed as an anticyanide agent. The test article was administered by daily gavage to male CD® rats for at least 60 days and to pregnant CD® rats for 23 - 27 days in sperm-positive females and for 48 days in sperm-negative females. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. All methods and procedures were conducted in accordance with the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Intl. Quality Assurance Programs designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was initiated on July 3, 1995; dosing began October 20, 1995 (males) and November 3, 1995 (females). The in-life portion was terminated on December 21, 1995 (last male necropsy).

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 Tartrate (Bottle No. BM19356), a yellow powder, was provided by the Sponsor and was received on August 31, 1995 from Herner & Co, Rockville, MD. The test article was previously assigned an in-house chemical number (1720614). The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL tartrate and the mole fraction of the base is 0.71. It was stored at -20 to -15°C, and stored in an amber bottle. The chemical structure follows.



WR242511 TARTRATE

The Analytical Chemistry Report and certificate of analysis are contained in Appendix 1. The test article was initially identified by GC-MS and the purity was 99.55 ± 0.01%. The terminal purity was 99.42 ± 0.22 %. Thus, the test article was stable under storage conditions.

3.2 Animals

One hundred ten male and 120 female Virus Antibody Free (VAF) time-mated CD® rats were obtained from Charles River Breeding Laboratories, Portage, MI on October 4, 1995 and October 18, 1995, respectively. The animals were ≈ 8 weeks old upon arrival at the UIC AAALAC-accredited animal facility (male date of birth August 9, 1995; female date of birth August 22, 1995). Each animal was given a study-unique quarantine/pretest number as a subcutaneously implanted microchip. During the randomization to treatment groups, each animal was re-assigned a unique animal number. The microchips were re-programmed and these latter test numbers appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, sex, and dose level. Cage cards were color-coded as a function of treatment group. Animals were singly housed in polycarbonate cages with Anderson Bed-a-cob bedding (Heinold Co., Kankakee, IL) in a temperature (65 - 78°F) and humidity (30 - 70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages with fresh bedding weekly.

Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) and tap water from an automatic watering system in which the room distribution lines were flushed daily were provided *ad libitum* from arrival until termination. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water conducted by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

All animals were examined daily during the 15 day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on study. Vaginal washings were performed in all females for 9 days during the quarantine/pretest period in order to determine which females were cycling normally. Vaginal washings were also performed during the precohabitation period to assess potential effects on treatment on the estrous cycle and during cohabitiation to determine positive evidence of mating. Near the end of the quarantine/pretest period, 100 animals of each sex were randomized by sex into the four treatment groups as shown in the following table. The males and normally cycling females were randomized using a computer-generated randomization program, stratified on the basis of body weight.

Group	No. of Animals Male	Female	Treatment	Dose Level (mg base/kg/day)	Dose Conc. (mg base/ml)	Dose Volume (ml/kg/day)
1	25	25	Vehicle	0	0	5
2	25	25	WR242511	0.3	0.06	5
3	25	25	WR242511	1.0	0.2	5
4	25	25	WR242511	3.0	0.6	5

Dose levels were selected on the basis of a range-finding developmental toxicity study in female rats (UIC/TRL Study No. 144) and a three month toxicity study in male and female rats (UIC/TRL Study No. 107).

The gavage dosing procedure was accomplished by the use of a rigid oral feeding needle. All animals received the control article by gavage for the last three days during week -1 to acclimate them to the dosing procedure. The dosing suspensions were administered daily to male rats for 29 days prior to cohabitation, during the entire 18 day cohabitation period, and for 13 - 15 days after cohabitation for a range of 60 - 62 dosing days. WR242511 Tartrate was administered daily to females for 15 days prior to cohabitation, during their cohabitation period, and from gestation days (GD) 0 to 6. GD0 was defined as the day sperm was observed in the vaginal washing, and females with a known GD0 were designated as sperm-positive. The majority of females became sperm-positive after 1 - 5 days of cohabitiation. For these females, the overall dosing period was 23 - 27 days: 15 days during precohabitation, 1 - 5 days during cohabitation, and 7 days during

gestation. Five females (one each at 0, 0.3, and 1 mg base/kg/day; two at 3 mg base/kg/day) did not have sperm in the vaginal washing and were designated as sperm negative. Since their GD0 was unknown, dosing and cohabitation of these females continued until pregnancy was subsequently confirmed by observation of a distended abdomen and/or palpation of fetuses *in utero*. The dosing period for these females was 48 days: 15 days during precohabitation and 33 days during cohabitation (i.e., until confirmation of pregnancy).

Test article stock suspensions (20 mg base/ml) were prepared weekly by adding the appropriate amount of the mole fraction of the base WR242511 Tartrate (adjusted for purity) with the required volume of control article (1.0% Methylcellulose/0.2% Tween 80) in a pre-calibrated beaker. Dosing suspensions were prepared daily by diluting the stock with additional vehicle to the appropriate concentrations, and were administered to the animals at a dosing volume of 5 ml/kg/day. The dosing suspensions were kept at 0 - 8°C. Samples of all dosing suspensions (including controls and stock suspensions) prepared on the first day of each week were analyzed prior to use. Only samples within 10% of their target concentration were used. Since the actual dosing suspensions were prepared daily from the stock, the suspensions were not analyzed after use. Stability data obtained from a previous study (UIC/TRL Study No. 107) indicated that the stock formulation of WR242511 Tartrate (BM05816) was stable for three weeks; and the dosing suspensions for the range of concentrations used in this study were stable for 48 hours. For comparative purposes, the stock formulation used in this study (WR242511 Tartrate, BM19356) was analyzed and also found to be stable for at least 10 days. The test article suspensions were considered to be homogeneous based on homogeneity data from a previous study (UIC/TRL Study No. 107).

Body weights were recorded for all animals at randomization in week -1. For males, body weights were recorded twice weekly (≈ every 3 - 4 days) during the dosing period. A final body weight was recorded on the day of scheduled necropsy. For females, body weights were recorded twice weekly (≈ 3 - 4 days) during the dosing period throughout the cohabitation phase. Once evidence of positive mating was detected (i.e., sperm in the vaginal washing), body weights for these sperm-positive females were obtained during the dosing period on GD0 - 6, and in the postdosing period on GD10, 13, and 16. Food consumption for males was measured during week -1 and twice weekly (≈ 3 - 4 days) during the dosing period except during cohabitation. Food consumption for females was measured during week -1 and twice weekly (≈ 3 - 4 days) during precohabitation. Food consumption was not measured during cohabitation. When positive evidence of mating was detected (i.e., sperm in the vaginal washing), food consumption for females was measured during the following intervals: GD0 - 3; 3 - 6; 6 - 10; 10 - 13; and 13 - 16. All animals were observed daily for clinical signs of toxicity approximately 1 - 2 hours after dosing, and in the morning after the completion of the dosing period for females. Animals were also observed twice daily (at least 6 hours apart) for moribundity/mortality. Moribund animals were sacrificed on the day of the observation.

Sperm-positive female rats were euthanized in random order by CO_2 asphyxiation on GD16. The five female rats (Nos. 128, 183, 234, 285, and 293) that were sperm-negative

were euthanized by CO_2 asphyxiation the day after pregnancy was confirmed (day 19 of cohabitation). The high dose females (Nos. 277, 282, 286, 289, 292, and 298) that had been randomly assigned for pairing with six males that were sacrificed moribund prior to the start of the cohabitation phase after confirmation that they were not needed for cohabitation with other high dose males. The necropsy for all females included opening the abdominal and thoracic cavities and grossly evaluating the viscera. The uterus and ovaries were removed from the body and examined. For gravid sperm-positive animals, the number of *corpora lutea* on each ovary was recorded. Additionally, the number and location of implantation sites, viable and nonviable fetuses, and resorptions were recorded consecutively from the distal end of the left uterine horn to the cervix and then from the distal end of the right uterine horn to the cervix. The number of *corpora lutea* and implantation sites were also recorded for gravid, sperm-negative animals. A viable fetus was defined as one which had pink, well vascularized tissue; a dark red placenta; and clean, reddish amniotic fluid. A nonviable fetus was defined as one that had white, non-vascularized tissue; a necrotic, green placenta; and cloudy, dark amniotic fluid. Uteri and ovaries from all females were saved in 10% neutral buffered formalin for possible histopathological evaluation. The Sponsor will provide written directions regarding the disposition of these tissues. Following gross necropsy examination, the carcass of each dam was discarded.

The males were euthanized in random order by CO_2 asphyxiation following a review and discussion with the Sponsor of the fertility and mating indices of the majority of females in all dose groups. The thoracic, abdominal, and pelvic cavities were opened and the viscera examined. Paired organ weights were collected from each animal for the testes, epididymides, and seminal vesicles. Prostate weights were also recorded, and brains were weighed for organ to brain weight comparisons. Both testes were retained in Bouin's fixative. The left epididymis, prostate, and both seminal vesicles from all animals and tissues with gross lesions (i.e., lungs) were retained in 10% neutral buffered formalin for possible histopathological evaluation. The Sponsor will provide written directions regarding the disposition of these tissues. The right epididymis was trimmed, frozen on dry ice, and temporarily stored at -70°C or less for subsequent sperm counts and sperm morphology assessment. Following gross necropsy examination, the carcass of each animal was discarded.

Sperm motility was assessed at the time of necropsy. Semen samples were evaluated utilizing the Hamilton Thorne Integrated Visual Optics System (IVOS) 10 Sperm analyzer. The motility sample was prepared from the vas deferens and was placed in a suspension medium containing PBS with 1% BSA (Bovine Serum Albumin). After a 3 minute swim out period, a 100 μ deep cannula was inserted into the media and a sample was drawn up. The cannula was inserted into the stage, and a general examination of the sperm sample was made on the computer monitor. Sperm samples were discarded after analysis.

Subsequent to the necropsy, the frozen epididymal samples were thawed, and the caudal section was weighed and minced. One or two drops of the sample was spread on a slide and stained with Eosin for sperm morphology assessment. The minced epididymal

samples were homogenized, and a 100 μL sample was added to a vial containing a florescent dye which stained the DNA in the sperm head. A sample was loaded into the IVOS, and the stained sperm heads were counted. Results were reported as total sperm count adjusted for caudal epididymis weight (10^6 sperm/g tissue). Sperm samples were discarded after analysis.

Six high dose males were sacrificed moribund by CO_2 asphyxiation on day 15 or 21. These animals were grossly examined externally and internally. Sperm assessments were not conducted on these animals; and the carcasses were discarded. Organs/tissues displaying gross lesions were retained in 10% neutral buffered formalin for possible histopathological evaluation. The Sponsor will provide written directions regarding the disposition of these tissues.

3.4 Statistical Analyses

Body weights, body weight gains, calculated daily food consumption, and male organ to brain weight ratios were analyzed by one-way analysis of variance. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons to the vehicle control group.

Sperm counts, sperm morphology, and sperm motility; the numbers of *corpora lutea* (C.L.), implantations, resorptions, viable and nonviable fetuses; and the percent preimplantation loss*, postimplantation loss** and total implantation loss,*** were compared using the Kruskal-Wallis test. If a significant effect was seen ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons to the vehicle control group.

*Preimplantation loss% = [(#C.L. - #implantations)/# C.L.] x 100
**Postimplantation loss% = [(#implantations - #live fetuses)/#implantations] x 100
***Total implantation loss% = [(#C.L. - # live fetuses)/#C.L.] x 100

The following reproductive indices were analyzed by Fischer's exact test:

Mating Index = (No. with evidence of mating/No. cohoused) x 100
Fertility Index = (No. pregnant/No. with evidence of mating) x 100

Sperm-negative, pregnant animals were included in the analysis of the numbers of *corpora lutea* and implantations, the percent preimplantation loss, and the mating and fertility indices.

In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk are no longer considered GLP compliant.

4. RESULTS

4.1 Dosage Formulation Analyses

The results of dosage formulation analyses are shown in Table 2. The Analytical Chemistry Report is in Appendix A.

All dosage formulations which were used were within 10% of their target concentration prior to use.

4.2 Mortality/Clinical Signs

The summary of clinical signs are presented in Tables 3.1 - 3.3. Individual clinical signs are in Appendices B, D, and E.

4.2.1 Males

Six high dose males were sacrificed moribund prior to the start of the cohabitation period. On day 15, male (No. 252) was sacrificed following body weight loss (45 g) and reduced food consumption as well as observations of rough coat and piloerection. There were no gross necropsy findings. Five other animals (Nos. 257, 261, 264, 267, and 273) were sacrificed moribund on day 21 following body weight loss (35 - 49 g) and reduced food consumption. Clinical signs in four of these animals included hunched posture and/or rough coat. A mottled liver was seen in animal No. 252. In another animal (No. 267), gross necropsy revealed an enlarged, pale, and mottled liver; an enlarged, dark kidney; and a urinary bladder filled with dark red fluid. In addition to the findings in the high dose males sacrificed moribund, clinical signs observed in eleven of the remaining nineteen high dose males included hunched posture, piloerection, dark material around nose, and/or rough coat. There were no mortalities or clinical signs in males in the control, low, or mid dose groups.

4.2.2 Females

There were no mortalities or clinical signs in female rats in any group.

4.3 Body Weights

The summaries of body weights and body weight gains are in Tables 4.1 - 4.3 and 5.1 - 5.3. Individualbody weight and body weight gains are included in Appendices B, D, and E.

4.3.1 Males

In males at 3 mg base/kg/day, reductions and losses in body weight gains noted on days 5 - 36 resulted in a significant reduction in total body weight gains. These alterations were accompanied by significantly reduced body weights noted on days 8 - 63. A spurious increase in body weight gains noted on day 47 was not biologically relevant.

In the 1 mg base/kg/day group, sporadic, nonsignificant decreases in body weight gains resulted in a significant reduction in total body weight gains. Administration of WR242511 Tartrate did not affect body weights in the 0.3 mg base/kg/day group.

4.3.2 Females

During the precohabitation period, high dose females exhibited significant reductions in body weight gains and body weights on days 5 and 12, respectively. Total body weight gains for the precohabitation phase were also reduced in high dose females. During the gestation period, females in the 3 mg base/kg/day group had a significant increase in body weight gains occurred between GD0 - 1 followed by a significant reduction over GD1 - 2. Body weights were reduced on all gestational days; these alterations were significant on GD0 and GD2 - 6. Administration of WR242511 Tartrate did not affect body weights in any other group during the precohabitation, cohabitation, or gestation periods.

4.4 Food Consumption

The summary of mean daily food consumption is presented in Tables 6.1 - 6.3. Individual food consumption data are shown in Appendix B, D, and E.

4.4.1 Males

Significant reductions in food consumption generally occurred throughout the study in the 3 mg base/kg/day group. Reductions seen during days 22 - 26 and 54 - 57 were apparently not significant due to greater variability at these intervals compared to other intervals. Food consumption was unaffected in the 1 or 0.3 mg base/kg/day groups.

4.4.2 Females

During the precohabitation period, food consumption was significantly reduced in the 3 mg base/kg/day group except during the day 8 - 12 interval. During gestation, food consumption was reduced in the high dose females during days 3 - 6. Food consumption was unaffected by treatment in the 1 and 0.3 mg base/kg/day groups during the precohabitation and gestation periods.

4.5 Cesarean-Section Data

The summary of the Cesarean-section data is in Table 7. Individual data are presented in Appendix F.

There were no effects of treatment on any evaluated parameters in any group.

4.6 Female Reproductive Indices and Gross Necropsy Observations

The summary of female reproductive indices is presented in Table 8. The individual data is shown in Appendix F.

Treatment with WR242511 Tartrate had no effects on estrous cycling , mating, or fertility. An increase in the length of the estrous cycle in the 1 mg base/kg/day group was attributed to slight increases in a few animals. However, the mating and fertility indices were 100% in all WR242511 Tartrate-treated groups. There were no gross necropsy observations in any group.

4.7 Male Reproductive Indices and Gross Necropsy Observations

The summary of male reproductive indices is in Table 9. The Sperm Analysis Report is in Appendix C.

There were no effects on sperm motility, count, or morphology in any WR242511 Tartrate-treated group. At 3 mg base/kg/day, significant reductions were noted in organ to brain weight ratios for the epididymis, seminal vesicles, and prostate. The testes to brain weight ratio was unaffected by at least 60 days of treatment with 3 mg base/kg/day of WR242511 Tartrate. Reproductive organ to brain weight ratios were not affected in the 1 and 0.3 mg base/kg/day groups. There were no gross necropsy observations in any group attributable to treatment with WR242511 Tartrate.

5. DISCUSSION

This study evaluated the toxic potential of WR242511 Tartrate on reproductive capability in CD® male and female rats. Doses of 0, 0.3, 1.0, and 3.0 mg base/kg/day were administered by daily gavage to male CD® rats for at least 60 days and to pregnant female CD® rats for 23 - 27 days in sperm-positive animals and for 48 days in sperm-negative females. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. The results are summarized in Table 1.

Lethality/toxicity was seen primarily in the high dose males; while only toxicity occurred in high dose females. One of 25 high dose males was sacrificed moribund on day 15 and 5/25 males were sacrificed moribund on day 21. Clinical signs in these and/or the remaining high dose animals included dark material around the nose, piloerection, hunched posture, and rough coat. Significant reductions in body weights, body weight gains, and food consumption occurred in males at 3 mg base/kg/day. In the 1 mg base/kg/day males, sporadic, nonsignificant reductions in body weight gains contributed to a significant reduction in total body weight gains. Decreased organ weight to brain weight ratios were noted in high dose males for the epididymis, seminal vesicles, and prostate. Spermatozoa in the testis are immature and incapable of fertilizing ova, and the accessory organs are critical to the process of sperm maturation, motility, and survival (Eddy, 1988). Also, since these organs are androgen-dependent, their weights are considered to be an indirect measure of circulating testosterone levels (Thomas, 1991). Testosterone levels were not measured in this study. In spite of reductions in accessory sex organ to brain weight ratios as well as observations of lethality and/or toxicity in the male animals, there were no effects on sperm motility, count, or morphology in any group, and no apparent effects on the males' ability to impregnate the females.

Females in the 3 mg base/kg/day group exhibited significantly reduced body weights and food consumption during the precohabitation and gestation periods. There were no effects on the Cesarean section parameters or estrous cycle parameters in any group. Both the mating and fertility indices were 100% in all WR242511 Tartrate groups. The NOEL for reproductive capability of males and females was 3 mg base/kg/day in spite of lethality and/or toxicity observed in both sexes at this dose level.

6. REFERENCES

1. Eddy, E.M. (1988). Duct system and accessory glands of the male reproductive tract. In *Physiology and Toxicology of Male Reproduction*, cpt. 3, pp35 - 69. Ed.: J.C. Lamb IV and P.M.D. Foster, Academic Press, San Diego.

2. Thomas, J.A. (1991). Toxic responses of the reproductive system. In *Casarett and Doull's Toxicology: The Basic Science of Poisons*, cpt. 16, pp484 - 520. Ed.: M.O. Amdur, J. Doull, and C.D. Klassen, 4th edition, Pergamon Press, New York.

7. PERSONNEL

Principal Investigator	Barry S. Levine, D.Sc., D.A.B.T.
Study Director	Debra L. Kirchner, Ph.D., D.A.B.T.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Sperm Assessment (PAI)	Michael D. Mercieca, B.S.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Ms. Soudabeh Soura, Ms. Nancy Dinger, and Mr. Mukesh Pitroda.

8. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

Table 1
ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Summary of Toxic Responses

Dose Level (mg base/kg/day)	0	0.3	1.0	3.0
Rats/Sex	25	25	25	25
Clinical Signs	-	NE	NE	SM(6M) DM(1M) HP(6M) PE(10M) RC(9M)
Body Weight Gain: M/F	-	NE/NE	↓/NE	↓/↓
Food Consumption: M/F	-	NE/NE	NE/NE	↓/↓
Female Cesarean Section Evaluations	-	NE	NE	NE
Female Estrous Cycle Evaluations	-	NE	NE	NE
Mating and Fertility Indices	-	NE	NE	NE
Male Sperm Assessment	-	NE	NE	NE
Male Organ to Brain Weight Ratios	-	NE	NE	↓EP ↓SV ↓PR

CONCLUSIONS

This study evaluated the toxic potential of WR242511 Tartrate on the reproductive capability of male and female CD®rats. Doses were 0.3, 1.0, and 3.0 mg base/kg/day administered by daily gavage to male CD® rats for at least 60 days and to pregnant female CD® rats for 23 - 27 days in sperm-positive animals and for 48 days in sperm-negative animals. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. Lethality/toxicity was seen primarily in the high dose males; while only toxicity occurred in high dose females. Six of 25 high dose males were sacrificed moribund on days 15 or 21. Clinical signs in these and/or the remaining high dose animals included dark material around the nose, piloerection, hunched posture, and rough coat. Significant reductions in body weights, body weight gains, and food consumption occurred in males primarily at 3 mg base/kg/day. In males at 1 mg base/kg/day, sporadic, nonsignificant reductions in body weight gains contributed to a significant reduction in total body weight gains. Decreased organ weight to brain weight ratios were noted in high dose males for the epididymis, seminal vesicles, and prostate. However, there were no effects on sperm motility, count, or morphology in any group, and no apparent effects on the males' ability to impregnate the females. Females in the 3 mg base/kg/day group exhibited significantly reduced body weights and food consumption during the precohabitation and gestation periods. There were no effects on the Cesarean section parameters or estrous cycle parameters in any group. Both the mating and fertility indices were 100% in all WR242511 Tartrate groups. The NOEL for reproductive capability of males and females was 3 mg base/kg/day in spite of lethality and/or toxicity observed in both sexes at this dose level.

SM = Sacrificed Moribund
DM = Dark Material Around Nose
HP = Hunched Posture
PE = Piloerection
RC = Rough Coat
NE = No Effect
↓ = Decreased
EP = Epididymis
SV = Seminal Vesicles
PR = Prostate

Table 2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

Dosage Formulation Analyses[a]

Target Concentration (mg base/ml)	Week 1	% Target	Week 2	% Target	Week 3	% Target
0.06	0.061 ± 0.001	101.7	0.056 ± 0.001	93.3	0.061 ± 0.002	101.7
0.2	0.216 ± 0.002	108	0.187 ± 0.009	93.5	0.199 ± 0.002	99.5
0.6	0.623 ± 0.002	103.8	0.576 ± 0.010	96	0.585 ± 0.002	97.5

Target Concentration (mg base/ml)	Week 4	% Target	Week 5	% Target	Week 6	% Target
0.06	0.057 ± 0.001	95	0.065 ± 0.001	108.3	0.062 ± 0.001	103.3
0.2	0.195 ± 0.004	97.5	0.211 ± 0.009	105.5	0.210 ± 0.003	105
0.6	0.601 ± 0.001	100.2	0.636 ± 0.005	106	0.632 ± 0.002	105.3

Target Concentration (mg base/ml)	Week 4	% Target	Week 5	% Target	Week 9	% Target
0.06	0.061 ± 0.001	101.7	0.061 ± 0.001	101.7	0.062 ± 0.002	103.3
0.2	0.216 ± 0.007	108	0.210 ± 0.001	105	0.207 ± 0.002	103.5
0.6	0.645 ± 0.009	107.5	0.639 ± 0.008	106.5	0.619 ± 0.003	103.2

[a]Mean ± standard deviation for triplicate runs

Table 3.1
ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 197M SEX: MALE

DOSE:	0	0.3	1	3	mg base/kg/day
GROUP:	1-M	2-M	3-M	4-M	
Scheduled Sacrifice	25	25	25	19	
Sacrificed Moribund	0	0	0	6	
Dark Material Around Nose	0	0	0	1	
Hunched Posture	0	0	0	6	
Piloerection	0	0	0	10	
Rough Coat	0	0	0	9	
Total Number of Animals	25	25	25	25	

Table 3.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

PRECOHABITATION AND COHABITATION PHASES

SUMMARY OF CLINICAL SIGNS

STUDY: 197F. SEX: FEMALE

DOSE:	0	0.3	1	3	mg base/kg/day
GROUP:	1-F	2-F	3-F	4-F	
Normal	25	25	25	25	
Sacrificed[a]	1	1	1	8	
Total Number of Animals	25	25	25	25	

[a]Includes six females in high dose group not paired in the cohabitation phase and sperm-negative, pregnant females in all groups.

TAble 3.3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

GESTATION PHASE

SUMMARY OF CLINICAL SIGNS

STUDY: 197 SEX: FEMALE

DOSE:	0	0.3	1.0	3.0	mg base/kg/day
GROUP:	1-F	2-F	3-F	4-F	
Scheduled Sacrifice	21	24	24	17	
Normal	21	24	24	17	
Total Number of Animals	24	24	24	17	

Table 4.1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 197M SEX: MALE

PERIOD	DOSE: / GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY -3	MEAN	339	339	339	339	
	S.D.	14.0	13.9	13.6	14.4	
	N	25	25	25	25	
DAY 1	MEAN	353	352	350	351	
	S.D.	16.4	14.2	17.0	16.2	
	N	25	25	25	25	
DAY 5	MEAN	376	376	373	369	
	S.D.	17.8	17.0	17.4	16.0	
	N	25	25	25	25	
DAY 8	MEAN	382	383	377	368*	
	S.D.	18.7	18.0	18.4	16.8	
	N	25	25	25	25	
DAY 12	MEAN	403	404	397	377*	
	S.D.	22.8	20.4	20.3	25.4	
	N	25	25	25	25	
DAY 15	MEAN	411	413	403	371*	
	S.D.	22.9	21.5	20.9	35.6	
	N	25	25	25	25	
DAY 19	MEAN	429	431	418	372*	
	S.D.	24.6	23.8	23.4	42.9	
	N	25	25	25	24	
DAY 22	MEAN	444	443	430	393*	
	S.D.	25.6	25.0	24.2	29.6	
	N	25	25	25	19	
DAY 26	MEAN	453	455	441	389*	
	S.D.	27.9	27.6	26.6	38.6	
	N	25	25	25	19	
DAY 29	MEAN	461	465	450	388*	
	S.D.	28.0	28.7	26.9	44.5	
	N	25	25	25	19	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 197M SEX: MALE

PERIOD	DOSE: GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY 33	MEAN	461	469	452	373*	
	S.D.	29.2	28.2	25.4	40.2	
	N	25	25	25	19	
DAY 36	MEAN	473	478	460	370*	
	S.D.	28.9	29.1	27.2	41.8	
	N	25	25	25	19	
DAY 40	MEAN	487	492	470	378*	
	S.D.	29.7	30.6	34.9	47.2	
	N	25	25	25	19	
DAY 43	MEAN	496	499	479	392*	
	S.D.	30.8	30.3	31.5	48.8	
	N	25	25	25	19	
DAY 47	MEAN	507	508	489	413*	
	S.D.	31.5	31.6	30.7	39.0	
	N	25	25	25	19	
DAY 50	MEAN	515	517	498	428*	
	S.D.	33.0	32.2	33.1	34.7	
	N	25	25	25	19	
DAY 54	MEAN	522	524	502	426*	
	S.D.	32.9	33.0	32.5	39.2	
	N	25	25	25	19	
DAY 57	MEAN	524	529	506	431*	
	S.D.	34.4	33.2	33.1	47.1	
	N	25	25	25	19	
DAY 61	MEAN	534	536	512	434*	
	S.D.	33.3	33.2	32.7	44.8	
	N	25	25	25	19	
DAY 62	MEAN	541	547	514	434*	
	S.D.	28.6	38.6	26.2	35.2	
	N	8	6	9	8	
DAY 63	MEAN	549	545	518	438*	
	S.D.	36.4	40.9	46.6	44.8	
	N	10	8	7	6	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 4.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

PRECOHABITATION AND COHABITATION PHASES

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 197F SEX: FEMALE

PERIOD	DOSE: / GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F	mg base/kg/day
DAY -3	MEAN	229	230	230	230	
	S.D.	10.4	10.3	10.2	10.2	
	N	25	25	25	25	
DAY 1	MEAN	238	237	235	236	
	S.D.	12.7	11.2	10.5	10.3	
	N	25	25	25	25	
DAY 5	MEAN	244	243	242	238	
	S.D.	15.3	12.0	10.7	12.1	
	N	25	25	25	25	
DAY 8	MEAN	248	248	246	240	
	S.D.	14.7	12.6	11.9	13.6	
	N	25	25	25	25	
DAY 12	MEAN	252	252	249	240*	
	S.D.	15.2	12.5	14.4	15.3	
	N	25	25	25	25	
DAY 15	MEAN	257	258	256	248	
	S.D.	16.4	12.7	13.3	14.3	
	N	25	25	25	25	
DAY 19	MEAN	280	253	280	--	
	S.D.	19.0	0.7	4.2	--	
	N	3	2	2	0	
DAY 22	MEAN	290	--	291	--	
	S.D.	17.3	--	0.0	--	
	N	3	0	1	0	
DAY 26	MEAN	322	--	305	--	
	S.D.	0.0	--	0.0	--	
	N	1	0	1	0	
DAY 29	MEAN	306	--	--	--	
	S.D.	0.0	--	--	--	
	N	1	0	0	0	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

Table 4.3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

GESTATION PHASE

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 197 SEX: FEMALE

PERIOD	DOSE: / GROUP:	0 1-F	0.3 2-F	1.0 3-F	3.0 mg base/kg/day 4-F
DAY 0	MEAN	262	262	262	245*
	S.D.	17.5	13.8	17.7	14.9
	N	21	24	24	17
DAY 1	MEAN	272	273	273	260
	S.D.	18.5	13.9	16.4	14.6
	N	21	24	24	17
DAY 2	MEAN	278	278	278	263*
	S.D.	18.8	14.0	16.0	14.6
	N	21	24	24	17
DAY 3	MEAN	281	282	281	265*
	S.D.	18.7	14.6	15.8	12.7
	N	21	24	24	17
DAY 4	MEAN	283	285	285	268*
	S.D.	19.0	15.1	16.4	13.6
	N	21	24	24	17
DAY 5	MEAN	288	289	289	272*
	S.D.	19.9	14.7	15.7	13.5
	N	21	24	24	17
DAY 6	MEAN	291	292	293	276*
	S.D.	19.6	15.3	18.2	12.9
	N	21	24	24	17
DAY 10	MEAN	312	313	315	301
	S.D.	22.5	17.3	17.0	15.5
	N	21	24	24	17
DAY 13	MEAN	326	328	331	318
	S.D.	23.5	17.6	20.3	14.3
	N	21	24	24	17
DAY 16	MEAN	352	352	356	345
	S.D.	24.8	19.2	25.0	20.8
	N	21	24	24	17

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 5.1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 197M SEX: MALE

PERIOD[a]	DOSE: GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY 5[b]	MEAN	22	24	23	19*	
	S.D.	4.1	4.2	3.4	3.4	
	N	25	25	25	25	
DAY 8	MEAN	6	7	5	-2*	
	S.D.	3.8	3.4	4.6	4.1	
	N	25	25	25	25	
DAY 12	MEAN	21	21	20	9*	
	S.D.	5.5	4.3	4.2	14.2	
	N	25	25	25	25	
DAY 15	MEAN	8	9	6	-5*	
	S.D.	3.6	3.3	3.8	14.2	
	N	25	25	25	25	
DAY 19	MEAN	18	18	15	-4*	
	S.D.	4.2	3.8	4.6	23.3	
	N	25	25	25	24	
DAY 22	MEAN	14	12	12	2*	
	S.D.	3.3	3.1	4.2	11.3	
	N	25	25	25	19	
DAY 26	MEAN	9	12	10	-4*	
	S.D.	6.5	3.7	5.3	13.5	
	N	25	25	25	19	
DAY 29	MEAN	8	11	10	-1*	
	S.D.	11.8	3.5	3.2	13.6	
	N	25	25	25	19	
DAY 33	MEAN	1	3	2	-15*	
	S.D.	10.9	4.7	5.6	19.3	
	N	25	25	25	19	
DAY 36	MEAN	12	9	8	-3*	
	S.D.	5.3	3.2	10.4	24.5	
	N	25	25	25	19	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 197M SEX: MALE

PERIOD[a]	DOSE: GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY 40	MEAN	14	14	11	8	
	S.D.	6.4	3.1	13.2	23.0	
	N	25	25	25	19	
DAY 43	MEAN	9	7	9	14	
	S.D.	4.5	3.2	14.5	12.0	
	N	25	25	25	19	
DAY 47	MEAN	11	9	10	22*	
	S.D.	3.5	3.4	7.4	18.7	
	N	25	25	25	19	
DAY 50	MEAN	8	9	10	15	
	S.D.	4.1	6.5	9.6	15.2	
	N	25	25	25	19	
DAY 54	MEAN	7	7	3	-2	
	S.D.	4.7	6.9	10.3	23.1	
	N	25	25	25	19	
DAY 57	MEAN	2	5	5	4	
	S.D.	7.9	5.4	4.8	18.9	
	N	25	25	25	19	
DAY 61	MEAN	11	7	5	4	
	S.D.	6.6	8.3	8.1	19.9	
	N	25	25	25	19	
TOTAL GAIN	MEAN	181	184	162*	81*	
	S.D.	22.5	22.0	21.7	37.9	
	N	25	25	25	19	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period

Table 5.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

PRECOHABITATION AND COHABITATION PHASES

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 197F SEX: FEMALE

PERIOD[a]	DOSE: GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F	mg base/kg/day
DAY 5[b]	MEAN	5	6	7	2*	
	S.D.	4.4	2.5	3.5	3.5	
	N	25	25	25	25	
DAY 8	MEAN	5	5	4	2	
	S.D.	6.3	5.1	5.8	3.9	
	N	25	25	25	25	
DAY 12	MEAN	4	4	4	1	
	S.D.	4.8	3.6	5.3	4.0	
	N	25	25	25	25	
DAY 15	MEAN	5	6	7	8	
	S.D.	5.0	4.5	5.2	5.1	
	N	25	25	25	25	
DAY 19	MEAN	18	6	15	--	
	S.D.	4.9	2.1	8.5	--	
	N	3	2	2	0	
DAY 22	MEAN	10	--	14	--	
	S.D.	3.1	--	0.0	--	
	N	3	0	1	0	
DAY 26	MEAN	17	--	14	--	
	S.D.	0.0	--	0.0	--	
	N	1	0	1	0	
DAY 29	MEAN	-16	--	--	--	
	S.D.	0.0	--	--	--	
	N	1	0	0	0	
TOTAL GAIN	MEAN	19	21	22	12*	
	S.D.	8.0	5.6	6.8	7.7	
	N	25	25	25	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

Table 5.3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

GESTATION PHASE

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 197 SEX: FEMALE

PERIOD[a]	DOSE: GROUP:	0 1-F	0.3 2-F	1.0 3-F	3.0 mg base/kg/day 4-F
DAY 1[b]	MEAN	10	10	11	15*
	S.D.	3.8	3.7	4.2	4.8
	N	21	24	24	17
DAY 2	MEAN	7	6	5	3*
	S.D.	3.8	3.6	3.3	2.9
	N	21	24	24	17
DAY 3	MEAN	3	3	3	2
	S.D.	3.2	4.3	3.8	4.1
	N	21	24	24	17
DAY 4	MEAN	2	4	4	2
	S.D.	3.6	4.1	3.4	3.9
	N	21	24	24	17
DAY 5	MEAN	5	4	4	5
	S.D.	2.6	3.3	3.3	2.7
	N	21	24	24	17
DAY 6	MEAN	3	4	4	4
	S.D.	3.1	3.5	5.2	4.2
	N	21	24	24	17
DAY 10	MEAN	21	20	23	25
	S.D.	5.1	4.8	5.1	6.3
	N	21	24	24	17
DAY 13	MEAN	14	15	16	16
	S.D.	4.6	6.2	6.3	5.1
	N	21	24	24	17
DAY 16	MEAN	25	24	24	27
	S.D.	4.8	6.2	9.0	9.2
	N	21	24	24	17
TOTAL GAIN	MEAN	90	90	93	99
	S.D.	13.0	13.2	14.3	13.9
	N	21	24	24	17

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period

[b]Baseline is day 0

Table 6.1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 197M SEX: MALE

PERIOD [a]	DOSE: GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY -3[b]	INTAKE (g)	29.6	29.2	29.0	28.8	
	S.D.	1.70	1.83	2.18	1.86	
	N	25	25	25	25	
DAY 1	INTAKE (g)	27.0	25.2	25.9	26.1	
	S.D.	8.22	4.96	1.96	2.11	
	N	25	25	25	25	
DAY 5	INTAKE (g)	27.9	27.9	27.8	26.7	
	S.D.	2.13	2.25	3.68	2.49	
	N	25	25	25	25	
DAY 8	INTAKE (g)	25.8	25.8	25.3	21.7*	
	S.D.	1.95	1.54	1.13	1.79	
	N	25	25	24	25	
DAY 12	INTAKE (g)	25.4	25.4	25.1	20.2*	
	S.D.	2.08	1.88	2.36	3.76	
	N	25	25	25	25	
DAY 15	INTAKE (g)	25.3	25.6	24.6	18.7*	
	S.D.	1.78	1.87	1.39	5.80	
	N	25	25	25	25	
DAY 19	INTAKE (g)	26.6	26.6	25.6	17.6*	
	S.D.	1.84	1.91	2.13	7.04	
	N	25	25	25	24	
DAY 22	INTAKE (g)	26.3	25.4	25.3	21.0*	
	S.D.	1.99	2.01	1.63	5.44	
	N	25	25	25	19	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

Table 6.1 (contd.)

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 197M SEX: MALE

PERIOD[a]	DOSE: GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M	mg base/kg/day
DAY 26	INTAKE (g)	27.4	27.4	27.2	21.4	
	S.D.	2.00	2.20	2.14	4.69	
	N	25	25	25	19	
DAY 29	INTAKE (g)	25.1	25.7	25.4	17.4*	
	S.D.	2.64	2.08	1.37	6.60	
	N	25	25	25	19	
DAY 36	INTAKE (g)	27.1	27.2	26.3	16.0*	
	S.D.	1.69	1.80	2.44	7.58	
	N	20	21	22	17	
DAY 40	INTAKE (g)	26.7	27.6	26.3	19.4*	
	S.D.	4.35	1.95	4.77	8.22	
	N	20	24	23	17	
DAY 43	INTAKE (g)	27.4	26.8	26.5	23.0*	
	S.D.	1.85	1.73	2.13	6.03	
	N	23	24	23	17	
DAY 47	INTAKE (g)	28.0	28.1	28.6	25.5*	
	S.D.	2.13	2.33	2.60	3.88	
	N	23	24	24	17	
DAY 50	INTAKE (g)	26.8	26.2	26.3	25.1	
	S.D.	1.83	2.51	2.38	4.92	
	N	24	24	24	17	
DAY 54	INTAKE (g)	28.4	27.1	28.8	24.3*	
	S.D.	1.99	4.59	4.79	6.73	
	N	25	25	25	19	
DAY 57	INTAKE (g)	25.3	25.8	25.1	20.9	
	S.D.	1.95	1.66	3.66	6.71	
	N	25	25	25	19	
DAY 61	INTAKE (g)	28.0	27.6	27.1	22.9*	
	S.D.	1.95	1.84	2.21	5.45	
	N	25	25	25	19	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals

Table 6.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

PRECOHABITATION PHASE

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 197F SEX: FEMALE

PERIOD[a]	DOSE: GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F	mg base/kg/day
DAY -3[b]	INTAKE (g)	20.9	18.9	19.5	20.0	
	S.D.	4.42	2.28	4.11	2.30	
	N	25	25	25	25	
DAY 1	INTAKE (g)	16.8	16.6	16.7	17.0	
	S.D.	1.70	1.34	2.03	0.96	
	N	25	25	25	25	
DAY 5	INTAKE (g)	19.9	18.9	19.8	17.3*	
	S.D.	3.17	1.86	5.46	1.45	
	N	25	25	23	25	
DAY 8	INTAKE (g)	18.1	17.6	16.9	14.7*	
	S.D.	2.00	1.27	1.66	1.71	
	N	25	25	25	25	
DAY 12	INTAKE (g)	21.4	20.6	22.0	20.2	
	S.D.	4.44	2.73	5.19	5.77	
	N	25	25	25	24	
DAY 15	INTAKE (g)	17.7	17.1	17.1	15.4*	
	S.D.	2.26	1.49	1.69	1.68	
	N	25	25	25	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

Table 6.3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

GESTATION PHASE

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 197 SEX: FEMALE

PERIOD[a]	DOSE: / GROUP:	0 1-F	0.3 2-F	1.0 3-F	3.0 mg base/kg/day 4-F
DAY 3[b]	INTAKE (g)	24.4	24.2	23.6	21.3
	S.D.	3.90	6.26	5.05	3.09
	N	21	24	24	17
DAY 6	INTAKE (g)	21.8	21.6	21.6	20.1*
	S.D.	2.36	2.09	1.44	1.62
	N	21	24	24	17
DAY 10	INTAKE (g)	24.3	24.2	24.5	23.6
	S.D.	3.67	3.62	2.48	1.89
	N	21	24	24	17
DAY 13	INTAKE (g)	24.1	24.3	25.2	25.6
	S.D.	2.38	2.43	2.31	1.94
	N	21	23	24	17
DAY 16	INTAKE (g)	26.0	25.6	25.8	26.3
	S.D.	3.49	2.20	2.66	2.39
	N	21	24	24	17

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day 0

Table 7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

Summary of Maternal Cesarean-Section Data
(Mean ± S.D.)

Dose Level (mg base/kg/day)	0.0	0.3	1.0	3.0
Total Number of Females/Group	25	25	25	19
Total Number of Surviving Females	25	25	25	19
Total Number of Pregnant Females	23	25	25	19
Implantation Sites[a]	16.4 ± 2.8	16.1 ± 1.7	16.4 ± 3.0	15.6 ± 2.2
Corpora Lutea[a]	19.4 ± 4.5	18.1 ± 2.6	19.5 ± 2.7	17.6 ± 3.0
Early Resorptions[a]	0.7 ± 0.8	0.7 ± 0.9	0.8 ± 1.2	0.8 ± 0.5
Late Resorptions[a]	0	0 ± 0.2	0.1 ± 0.3	0.1 ± 0.2
Viable Fetuses[a]	16.2 ± 2.1	15.3 ± 1.9	15.4 ± 3.7	14.9 ± 2.0
Nonviable Fetuses[a]	0.1 ± 0.5	0.1 ± 0.4	0	0
Preimplantation Loss %[a,b]	11.9 ± 17.7	9.9 ± 10.9	14.6 ± 16.5	10.6 ± 8.6
Postimplantation Loss %[a,c]	4.2 ± 4.9	5.2 ± 6.8	8.3 ± 19.7	5.3 ± 4.2
Total Implantation %[a,d]	13.2 ± 10.7	14.2 ± 10.5	19.5 ± 19.8	14.5 ± 9.6

[a]Parameters statistically analyzed using the Kruskal-Wallis test ($p \leq 0.05$).

[b]Preimplantation Loss % = [(# Corpora Lutea - # Implants)/ # Corpora Lutea] x 100
[c]Postimplantation Loss % = [(# Implants - # Viable Fetuses)/ # Implants] x 100
[d]Total Implantation Loss/Litter = [(# Corpora Lutea - # Viable Fetuses)/ # Corpora Lutea] x 100

Table 8

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
TOXICITY STUDY OF WR242511 TARTRATE IN RATS

Summary of Female Reproductive Data

Dose Level (mg base/kg/day)	0	0.3	1.0	3.0
Estrus Cycle Data[a] No. (%) Cycling	25 (100%)	24 (96%)	24 (96%)	23 (92%)
Average No. Occurrences of Estrus[b]	3.84 ± 0.46	3.79 ± 0.58	3.50 ± 0.50	3.70 ± 0.46
Average Length of Estrus Cycle[b]	3.92 ± 0.46	4.08 ± 0.58	4.31 ± 0.62	3.88 ± 0.28
Mating Index[c,e]	100%	100%	100%	100%
Fertility Index[d,e]	92%	100%	100%	100%

[a]For the 15 day precohabitation period
[b]Mean ± S.D.
[c]Mating Index = (No. with evidence of mating/No. cohoused) x 100
[d]Fertility Index = (No. pregnant/No. with evidence of mating) x 100
[e]Statistically analyzed using the Fisher's Exact Test

Table 9

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
TOXICITY STUDY OF WR242511 TARTRATE IN RATS

Summary of Male Reproductive Data

Dose Level (mg base/kg/day)	0	0.3	1.0	3.0
Sperm Analysis Data[a,b] Percent Sperm Motility[a]	94.48 ± 19.87 (25)	97.92 ± 2.60 (25)	98.92 ± 1.04 (25)	98.33 ± 1.46 (18)
Sperm Count[a,b]	876.32 ± 404.73 (25)	893.56 ± 352.10 (25)	890.87 ± 360.81 (25)	835.56 ± 419.95 (19)
Sperm Morphology[c]	1.03 ± 1.16 (25)	0.86 ± 1.10 (25)	1.13 ± 2.21 (25)	0.81 ± 0.95 (19)
Organ: Brain Weight Ratios[a] Epididymis[a]	0.64 ± 0.06 (25)	0.65 ± 0.04 (25)	0.66 ± 0.05 (25)	0.60 ± 0.06* (19)
Seminal Vesicles[a]	0.87 ± 0.16 (25)	0.93 ± 0.21 (25)	0.85 ± 0.16 (25)	0.60 ± 0.06* (19)
Prostate[a]	0.49 ± 0.12 (25)	0.50 ± 0.08 (25)	0.46 ± 0.07 (25)	0.35 ± 0.08* (19)
Testes[a]	1.62 ± 0.14 (25)	1.65 ± 0.09 (25)	1.64 ± 0.16 (25)	1.62 ± 0.20 (19)

[a]Mean ± SD; (N) = Number evaluated
[b]Statistically analyzed using the Kruskal-Wallis test ($P \leq 0.05$)
[c]Million sperm/g caudal epididymal tissue
*Statistically significant from control group using ANOVA/Dunnett's test ($P \leq 0.05$)

DRAFT

APPENDIX A

ANALYTICAL CHEMISTRY REPORT

DRAFT

Oral Fertility and Early Embryonic Development
Study of WR242511 Tartrate in Rats
UIC/TRL Study Number 197

Part I: **Identity and Purity Study of WR242511 Tartrate**

Part II: **Stability of WR242511 Tartrate in 1% Methylcellulose/0.2% Tween 80 Suspensions**

Part III: **Dosing Formulations Analysis of WR242511 Tartrate in 1% Methylcellulose/0.2% Tween 80**

Analysts: Adam Negrusz
A. Karl Larsen, Jr.
Thomas Tolhurst

Study Site: Drug Disposition Research Laboratory
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

Sponsor: Toxicology Research Laboratory
University of Illinois at Chicago
Chicago, Illinois 60612

Report Prepared by: Thomas Tolhurst T. Tolhurst

Report Prepared: April 1, 1996

Approved: April 1, 1996
Eugene F. Woods E. Woods
Drug Disposition Research Laboratory

DRAFT

Part 1: Identity and Purity of WR242511 Tartrate

Objective

The objective of this study was to confirm the identity and establish the purity of WR242511 Tartrate.

Identification

GC-MS System

Gas Chromatograph:	Hewlett-Packard Series 11
Mass Selective Detector:	Hewlett-Packard Model 5970
Analytical Column:	30 m x 0.25 mm ID, DB-5 with a 3 micron film thickness.
GC Parameters:	injector temp. 250° C, oven temp. 70° C initial, 280° C final, 15° C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR242511 Tartrate) was submitted by the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 0.71 μg base/ml and a 2 μl aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at rate of 1 scan per second.

Results

The mass spectrum indicates a molecular ion m/e 373 which is in agreement with the WR242511 free base molecular weight. Major fragments of WR242511 Tartrate sample are m/e 84, 175, 203, 288.

Figure 1 shows the mass spectrum of the WR242511 Tartrate sample.

Purity

Experimental

The subject sample (WR242511 Tartrate) was supplied by the Toxicology Research Laboratory and stored at -20° C when not being analyzed.

DRAFT

Description

A fine yellow powder, no obvious odor.

HPLC System

Solvent Delivery System:	Water Model 510 Pump
Injector:	Rheodyne 7125 with 50 μl sample loop
Analytical Column:	Spherisorb CN 5μ, 250 mm x 4.6 mm (Alltech)
Detector:	Perkin-Elmer LC-55B UV Detector, 230 nm, 264 nm
Integrator:	Spectra-Physics SP4270 Integrator
Mobile Phase:	20% methanol, 50% acetonitrile, 30% 0.01 M ammonium formate (in water), pH 3.0 (adjusted with 88% formic acid), flow 1.5 ml/minute

Procedure

Six solutions of WR242511 Tartrate were prepared as follows. Twenty five mg of WR242511 Tartrate sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. An aliquot of each solution was immediately chromatographed at 230 nm and next at 264 nm.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR242511 Tartrate and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR242511 Tartrate present in the sample:

$$\%\text{PURITY} = (\text{area of WR242511 Tartrate/total area}) \times 100$$

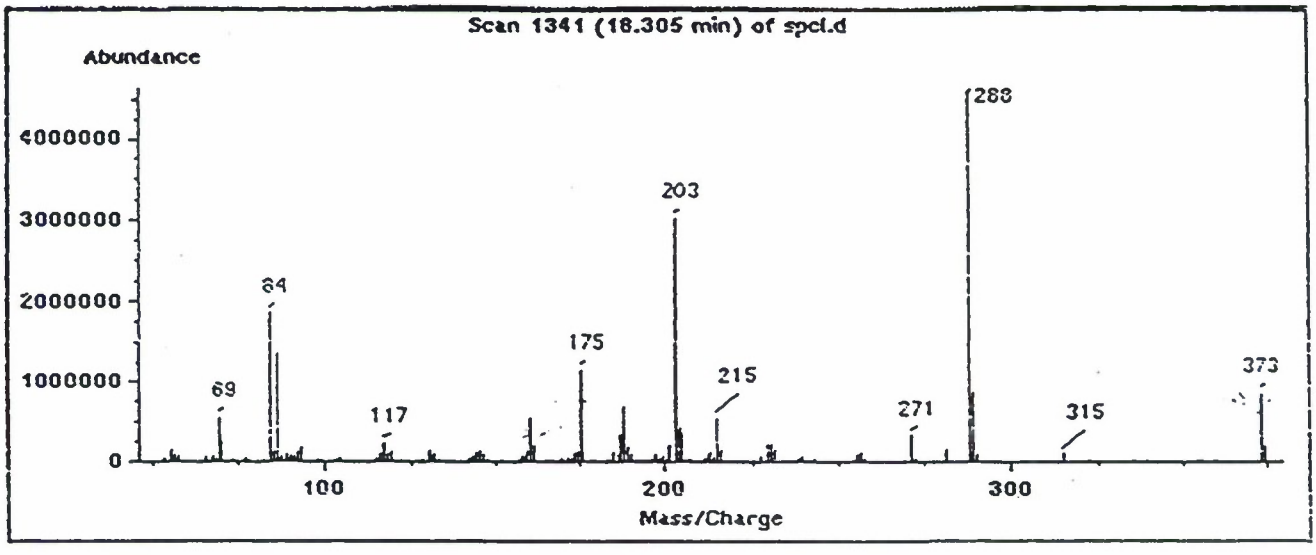
Results

Typical chromatograms are shown in Figure 2. The subject samples were found to contain less than 1% of one UV-absorbing impurity (230 nm). At 264 nm no visible impurities were observed. The mean percent purity of the initial WR242511 Tartrate sample was found to be 99.55% ($\pm$ 0.01%); terminal mean purity was 99.4% ($\pm$ 0.22%). The assay results are presented in Tables 1 and 2.

DRAFT

Figure 1

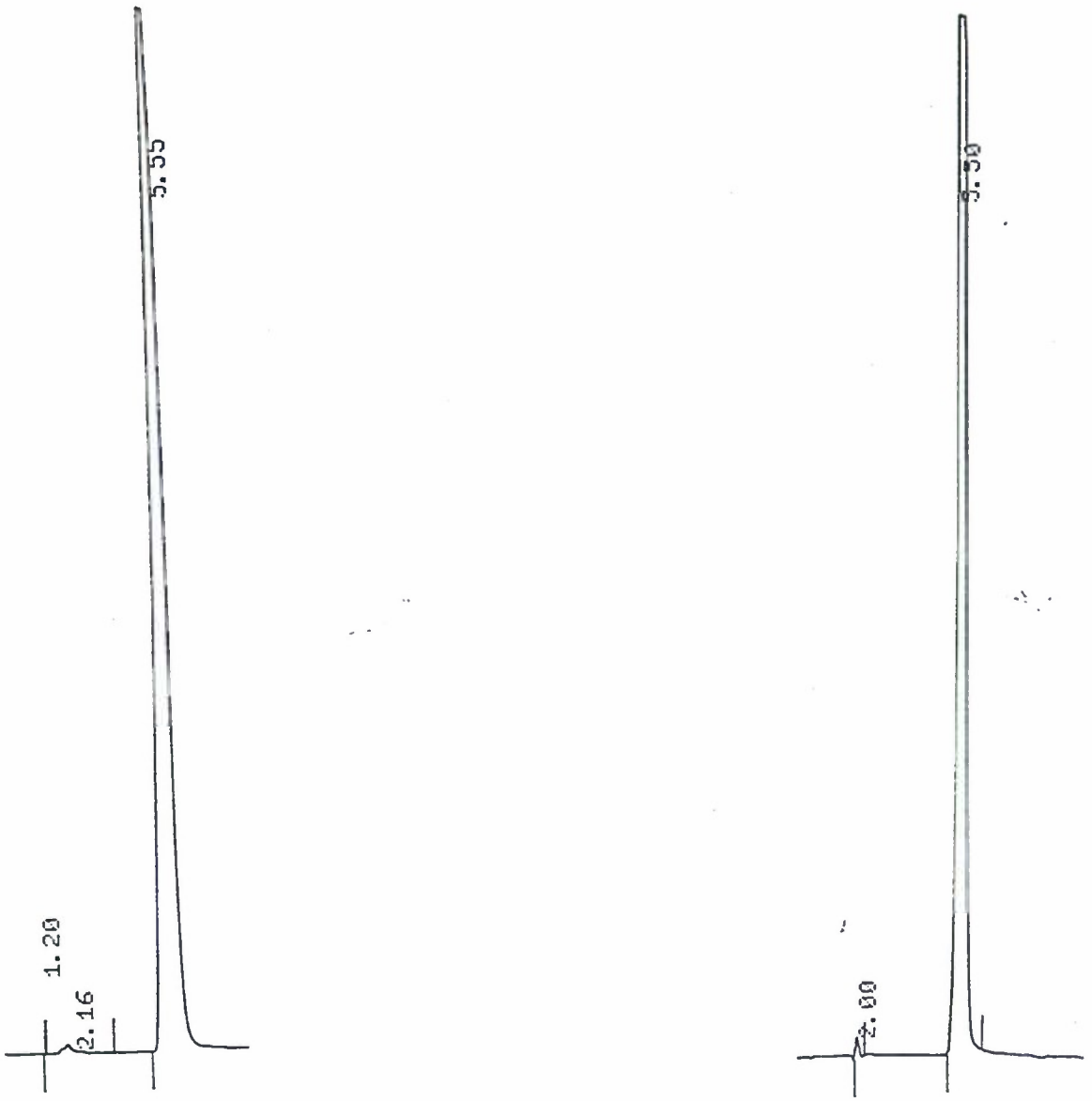
Mass Spectrum of WR242511 Tartrate Sample



DRAFT

Figure 2

Chromatograms of WR242511 Tartrate Sample,
(conc. 0.71 mg base/ml)
A - Inital Sample, B - Terminal Sample



A B

DRAFT

Table 1

Purity Data for WR242511 Tartrate
Initial Sample

Solutions

Peak Identitiy	1	2	3	4	5	6
A	2921	2698	2663	2668	2746	2662
WR242511	606009	606033	610130	604792	603617	606638
%Purity	99.52	99.56	99.57	99.56	99.55	99.57

Mean ± S.D. - 99.55 ± 0.01%

DRAFT

Table 2

Purity Data for WR242511 Tartrate
Terminal Sample

Solutions

Peak Identitiy	1	2	3	4	5	6
A	135271	130110	144495	135293	303108	178341
WR242511	29518697	29446855	29434872	29713801	29448011	29522279
%Purity	99.54	99.56	99.51	99.55	98.98	99.40

Mean ± S.D. - 99.42 ± 0.22%

Part II: Stability of WR242511 Tartrate in 1% Methylcellulose/0.2% Tween 80 Suspensions

Introduction

Five suspensions of WR242511 Tartrate in 1% methylcellulose/0.2% Tween 80 were submitted by the Toxicology Research Laboratory for stability testing. Four of the suspensions (0.06, 0.2, 0.6 and 20 mg base/ml) were prepared using Lot BM19356 and one suspension (20 mg base/ml) was prepared using Lot BM 05816. Of the five suspensions, three suspensions (0.06, 0.2 and 0.6 mg base/ml) were analyzed at 0, 24 and 48 hours. The remaining two suspensions were analyzed at 0, 5, and 10 days. All suspension were stored at 4°C (± 2 °C) for the duration of the study.

Analytical Method

Reagents

Subject sample (WR242511 Tartrate) was supplied by Toxicology Research Laboratory. HPLC grade methanol, acetonitrile, ammonium formate and formic acid were purchased from Fisher Scientific. HPLC grade water was supplied through a Millipore, MILLI-Q Reagent Water System which was fed with distilled water.

Standards

All WR242511 concentrations reflect free base value. A 0.71 mg base/ml WR242511 stock solution was prepared by weighing 100 mg of DL-tartrate salt (mole fraction = 0.71) into a 100 ml volumetric flask. The content was dissolved in and the volume brought to mark with mobile phase. A working calibration standard solution of 71 μg base/ml was prepared by transferring 10.0ml of the 0.71 mg base/ml stock solution to a 100 ml volumetric flask and diluting to mark with mobile phase. The remaining working calibration standards were prepared from the 71 μg base/ml WR242511 solution as follows:

Volume Transferred (ml)	Flask Volume (ml)	Final Concentration (μg base/ml)
1.0	10	7.1
2.0	10	14.2
4.0	10	28.4
6.0	10	42.6
8.0	10	56.8

Controls

Control A (0.71 mg base/ml) and control B (2.1 mg base/ml) were prepared by weighing 25 mg, and 75 mg respectively of WR242511 Tartrate DL-tartrate salt into two 25 ml volumetric flasks. The contents were dissolved in and diluted to mark with mobile phase.

DRAFT

Sample Preparation

Stability suspensions submitted by the Toxicology Research Laboratory and stored under refrigeration were allowed to warm to room temperature and mixed prior to diluting. Three 1 ml aliquots were withdrawn from each sample and transferred to individual volumetic flasks. The contents of each volummetric flask was dissolved in and diluted to mark with mobile phase. The stability suspensions at 20 mg/ml were further diluted such that the final concentration was within the range of the standard curve (7.1 - 71 μg/ml). Final dilutions were 1:2.5, 1:10, 1:25 and 1:625 for the 0.06, 0.2, 0.6 and 20 mg base/ml suspensions, respectively.

HPLC System

Solvent Delivery System:	Water Model 510 Pump
Injector:	Rheodyne 7125 with 50μl sample loop
Analytical Column:	Spherisorb CN 5μ, 250 mm x 4.6 mm (Alltech)
Detector:	Perkin-Elmer LC-55B UV Detector, 230 nm, 264 nm
Integrator:	Spectra-Physics SP4270 Integrator
Mobile Phase:	20% methanol, 50% acetonitrile, 30% 0.01 M ammonium formate (in water), pH 3.0 (adjusted with 88% formic acid), flow 1.5 ml/minute

Calculations

A standard curve was run at the beginning and the end of each assay day. Final concentration for controls and samples were determined using a composite standard curve. The composite standard curve was determined by linear least squared regression analysis of the peak areas for WR242511 Tartrate as a function of concentration. WR242511 Tartrate concentrations (mg base/ml) for controls and samples were determined using the following equation:

$$\text{WR242511 conc.} = (Y-B)/M \times (\text{d.f.}/1000)$$

Y = peak height

B = Y-intercept from composite standard curve

M = slope from composite standard curve

d.f. = dilution factor

DRAFT

The standard curves were linear over the range of WR242511 assayed (7.1 μg base/ml - 71 μg base/ml) and had a mean for the regression coefficient of 0.999. A representative standard curve is shown in Figure 3.

Data Analysis

The stability of WR242511 Tartrate in 1% methylcellulose/0.2% Tween 80, stored at 4°C was assessed by examining the percentage change from baseline concentration over time. A change from baseline concentration of greater than 10% was considered to represent a significant loss of potency.

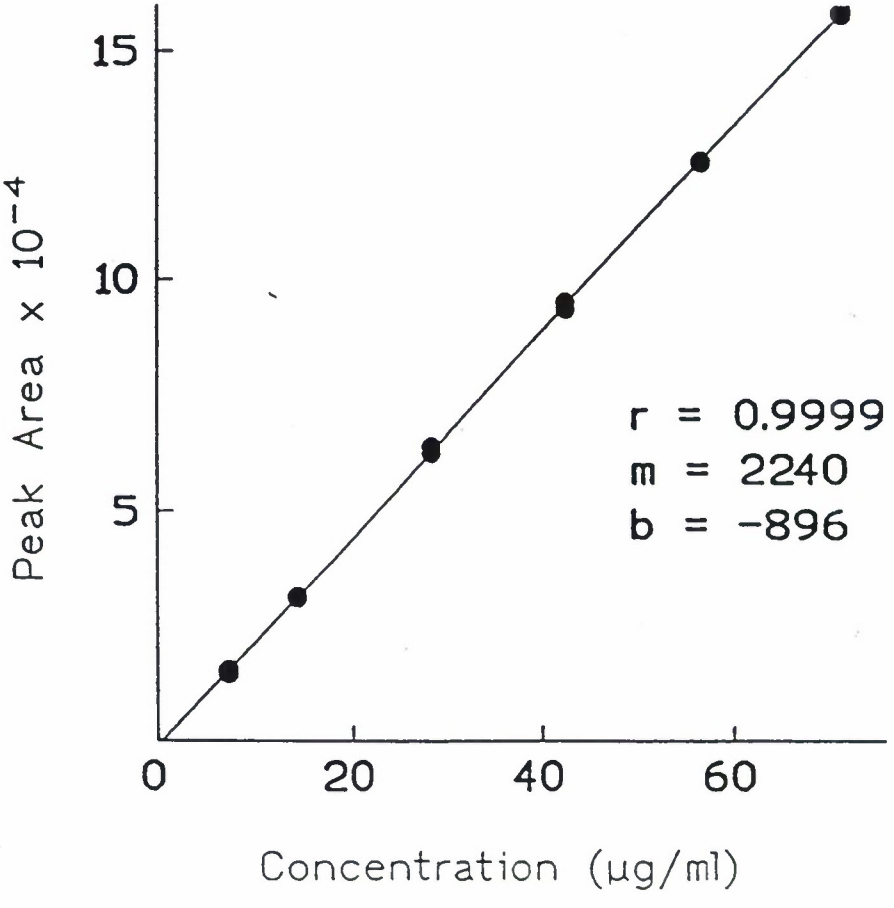
Results

The results of the stability testing of WR242511 Tartrate in 1% methylcellulose/0.2% Tween 80 are summarized in Tables 3 and 4 and Figures 4 and 5. There was no loss of potency observed as defined by a decrease from baseline concentration of greater than 10% over the time interval studied. No difference in potency was observed between WR242511 Tartrate lots BM19356 and BM05816.

DRAFT

Figure 3

Standard Curve for WR242511



DRAFT

Table 3

Stability of WR242511 Tartrate Suspensions, Lot No. BM 19356 (storage at 4° C)

	Time (days) 0	1	2
Mean WR242511 Conc. (mg base/ml)	0.049	0.047	0.047
Standard Deviation	± 0.0002	± 0.0006	± 0.0001
% of Baseline Conc.	100	95.6	95.9
Mean WR242511 Conc. (mg base/ml)	0.164	0.152	0.150
Standard Deviation	± 0.0002	± 0.0024	± 0.0005
% of Baseline Conc.	100	92.7	91.5
Mean WR242511 Conc. (mg base/ml)	0.501	0.478	0.460
Standard Deviation	± 0.0025	± 0.0035	± 0.0054
% of Baseline Conc.	100	95.4	91.8

DRAFT

Table 4

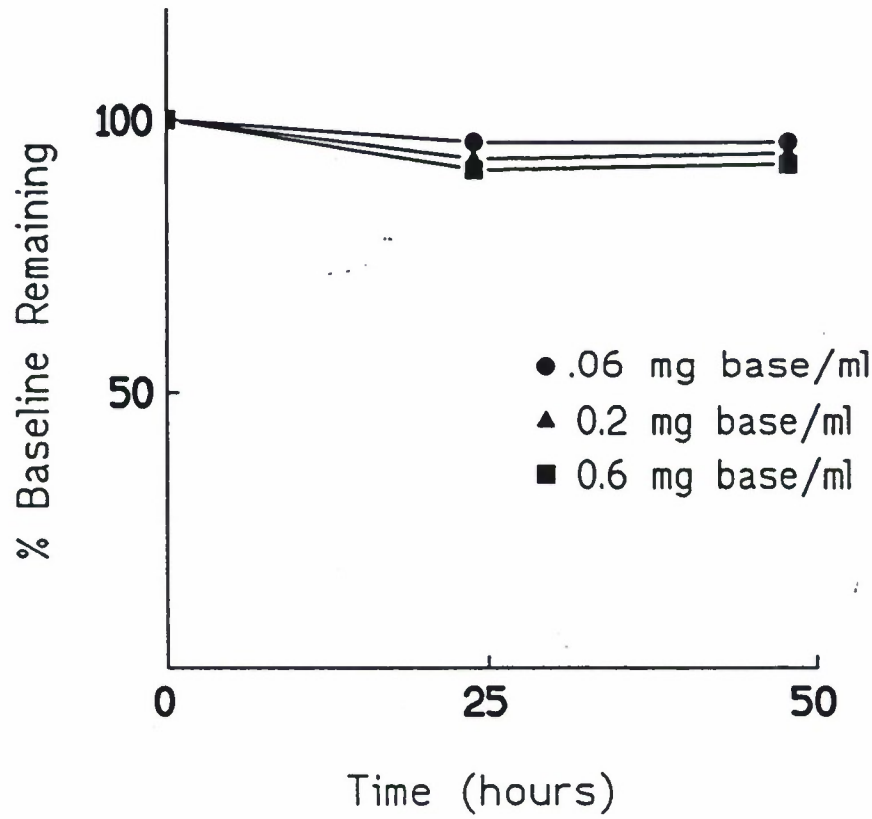
Stability of WR242511 Tartrate Suspensions
(conc. 20 mg base/ml, storage at 4° C)

	Time (days)		
WR242511 lot BM 19356	0	5	10
Mean WR242511 Conc. (mg base/ml)	21.925	21.901	21.649
Standard Deviation	± 0.173	± 0.144	± 0.046
% of Baseline Conc.	100	99.9	98.7
WR242511 lot BM05816	0	5	10
Mean WR242511 Conc. (mg base/ml)	20.676	20.249	20.599
Standard Deviation	± 0.159	± 0.085	± 0.117
% of Baseline Conc.	100	97.9	99.6

DRAFT

Figure 4

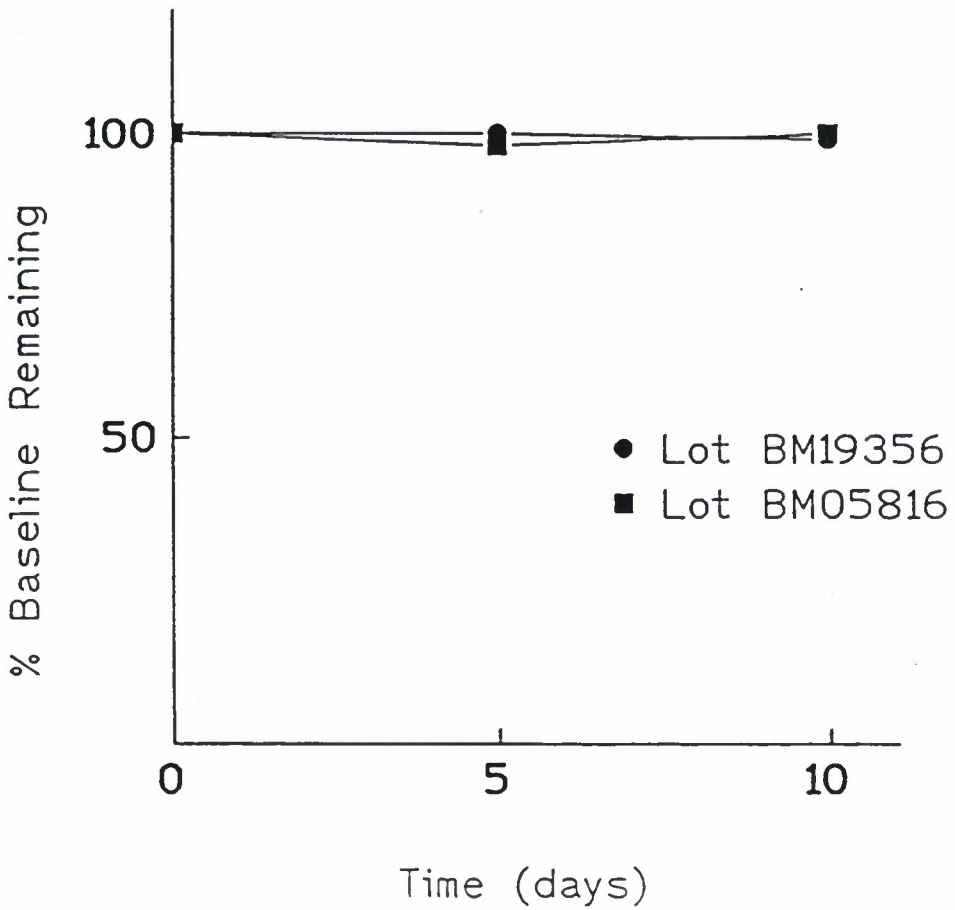
Stability of WR242511 (Lot# BM19356) in Suspension



DRAFT

Figure 5

Stability of WR242511 in Suspension
(20 mg base/ml)



Part III: Dosing Formulations Analysis of WR242511 Tartrate in 1% Methylcellulose/0.2% Tween 80

Introduction:

Samples from UIC/TRL Study No. 197 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of WR242511 free base in dosing formulations. Samples were received on October 20, and 27, 1995; November 3, 10, 17 and 22, 1995 and December 1, 8 and 15, 1995. All samples submitted were analyzed by HPLC using existing analytical method (SOP No. 01MA05-01).

Analytical Method

Regents

See Part II: Analytical Method

Standards

See Part II: Analytical Method

Controls

See Part II: Controls

Sample Preparation

Triplicate dilutions of each suspension were prepared in mobile phase prior to HPLC analysis. The vehicle and 0.06 mg base/ml suspension was diluted 1:2.5 by transferring 2 ml of suspension to individual 5 ml volumetric flasks. The contents were dissolved in and diluted to mark with mobile phase. The 0.2 and 0.6 mg base/ml suspensions were diluted 1:5 and 1:10, respectively.

HPLC System

See Part I: HPLC System

Results

Results of dosing formulations analysis for UIC/TRL Study No. 197 are presented in Table 5, 6 and 7. All suspensions used in UIC/TRL Study No. 197 were within acceptable limits (± 10% of target concentration).

DRAFT

Table 5

Results of Dosing Formlations Analysis for UIC/TRL Study No. 197

October 20, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.061 ± 0.001
BLUE	0.2	0.216 ± 0.002
BROWN	0.6	0.623 ± .0.002

October 27, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.056 ± 0.001
BLUE	0.2	0.187 ± 0.009
BROWN	0.6	0.576 ± 0.010

November 3, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.061 ± 0.002
BLUE	0.2	0.199 ± 0.002
BROWN	0.6	0.585 ± 0.002

DRAFT

Table 6

Results of Dosing Formulations Analysis for UIC/TRL Study No. 197

November 10, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.057 ± 0.001
BLUE	0.2	0.195 ± 0.004
BROWN	0.6	0.601 ± 0.001

November 17, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.065 ± 0.001
BLUE	0.2	0.211 ± 0.009
BROWN	0.6	0.636 ± 0.005

November 22, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.062 ± 0.001
BLUE	0.2	0.210 ± 0.003
BROWN	0.6	0.632 ± 0.002

DRAFT

Table 7

Results of Dosing Formulations Analysis for UIC/TRL Study No. 197

December 01, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.061 ± 0.001
BLUE	0.2	0.216 ± 0.007
BROWN	0.6	0.645 ± 0.009

December 08, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.061 ± 0.001
BLUE	0.2	0.210 ± 0.001
BROWN	0.6	0.639 ± 0.008

December 15, 1995

Sample Identification	Taget Concentrations (mg base/ml)	Mean Concentrations ± S.D. (mg base/ml)
WHITE	0.0	0.0
PINK	0.06	0.062 ± 0.002
BLUE	0.2	0.207 ± 0.002
BROWN	0.6	0.619 ± 0.003

DRAFT

APPENDIX B

INDIVIDUAL MALE DATA

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 1-M SEX: MALE
DAY 1-DAY 63 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
101	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
102	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
103	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
104	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
105	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
106	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
107	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
108	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
109	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
110	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
111	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
112	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
113	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 1-M SEX: MALE
DAY 1-DAY 63 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
114	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
115	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
116	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
117	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
118	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
119	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
120	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
121	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
122	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
123	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
124	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
125	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 2-M SEX: MALE
DAY 1-DAY 63 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
151	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
152	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
153	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
154	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
155	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
156	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
157	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
158	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
159	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
160	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
161	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
162	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
163	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 2-M SEX: MALE
DAY 1-DAY 63 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
164	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
165	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
166	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
167	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
168	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
169	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
170	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
171	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
172	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
173	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
174	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
175	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 3-M SEX: MALE
DAY 1-DAY 63 DOSE: 1 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
201	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
202	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
203	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
204	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
205	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
206	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
207	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
208	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
209	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
210	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
211	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
212	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
213	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 3-M SEX: MALE
DAY 1-DAY 63 DOSE: 1 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
214	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
215	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
216	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
217	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
218	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
219	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
220	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
221	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
222	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
223	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
224	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
225	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 4-M SEX: MALE
DAY 1-DAY 63 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
251	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
252	Normal			DAY 1-DAY 11
	Piloerection			DAY 12
	Rough Coat			DAY 13-DAY 14
	Sacrificed Moribund			DAY 15
253	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
254	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
255	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
256	Normal			DAY 1-DAY 26
	Normal			DAY 28-DAY 32
	Normal			DAY 34-DAY 61
	Piloerection			DAY 27
	Piloerection			DAY 33
	Scheduled Sacrifice			DAY 62
257	Hunched Posture			DAY 20-DAY 21
	Normal			DAY 1-DAY 18
	Rough Coat			DAY 19-DAY 21
	Sacrificed Moribund			DAY 21
258	Normal			DAY 1-DAY 31
	Normal			DAY 33-DAY 61
	Piloerection			DAY 32
	Scheduled Sacrifice			DAY 62
259	Normal			DAY 1-DAY 57
	Normal			DAY 59-DAY 62
	Piloerection			DAY 58
	Scheduled Sacrifice			DAY 63

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 4-M SEX: MALE
DAY 1-DAY 63 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
260	Hunched Posture			DAY 24
	Hunched Posture			DAY 26-DAY 27
	Normal			DAY 1-DAY 19
	Normal			DAY 33-DAY 57
	Normal			DAY 59-DAY 60
	Piloerection			DAY 58
	Rough Coat			DAY 20-DAY 32
	Scheduled Sacrifice			DAY 61
261	Hunched Posture			DAY 21
	Normal			DAY 1-DAY 20
	Rough Coat			DAY 21
	Sacrificed Moribund			DAY 21
262	Normal			DAY 1-DAY 22
	Normal			DAY 25-DAY 32
	Normal			DAY 34-DAY 41
	Normal			DAY 48-DAY 61
	Piloerection			DAY 33
	Rough Coat			DAY 23-DAY 24
	Rough Coat			DAY 42-DAY 47
	Scheduled Sacrifice			DAY 62
263	Normal			DAY 1-DAY 62
	Scheduled Sacrifice			DAY 63
264	Hunched Posture			DAY 20-DAY 21
	Normal			DAY 1-DAY 18
	Rough Coat			DAY 19-DAY 21
	Sacrificed Moribund			DAY 21
265	Dark Material Around Nose			DAY 33
	Normal			DAY 1-DAY 32
	Normal			DAY 34-DAY 61
	Scheduled Sacrifice			DAY 62
266	Normal			DAY 1-DAY 34
	Normal			DAY 39-DAY 60
	Piloerection			DAY 35-DAY 38
	Scheduled Sacrifice			DAY 61

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 4-M SEX: MALE
DAY 1-DAY 63 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
267	Hunched Posture			DAY 20
	Normal			DAY 1-DAY 18
	Rough Coat			DAY 19-DAY 20
	Sacrificed Moribund			DAY 21
268	Normal			DAY 1-DAY 34
	Normal			DAY 39-DAY 61
	Piloerection			DAY 35-DAY 38
	Scheduled Sacrifice			DAY 62
269	Normal			DAY 1-DAY 61
	Scheduled Sacrifice			DAY 62
270	Hunched Posture			DAY 24-DAY 25
	Normal			DAY 1-DAY 20
	Normal			DAY 22
	Normal			DAY 26
	Normal			DAY 28
	Normal			DAY 46-DAY 62
	Piloerection			DAY 27
	Rough Coat			DAY 21
	Rough Coat			DAY 23-DAY 25
	Rough Coat			DAY 29-DAY 45
	Scheduled Sacrifice			DAY 63
271	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61
272	Normal			DAY 1-DAY 26
	Normal			DAY 28-DAY 61
	Piloerection			DAY 27
	Scheduled Sacrifice			DAY 62
273	Normal			DAY 1-DAY 21
	Sacrificed Moribund			DAY 21
274	Normal			DAY 1-DAY 60
	Scheduled Sacrifice			DAY 61

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197M GROUP: 4-M SEX: MALE
DAY 1-DAY 63 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
275	Normal			DAY 1-DAY 22
	Normal			DAY 39-DAY 61
	Rough Coat			DAY 23-DAY 38
	Scheduled Sacrifice			DAY 62

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 1					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 2					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 3					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 4					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 5					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 6					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 7					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 8					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 9					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 10					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 11					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 12					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%
Piloerection		0	0	0	1 4%
DAY 13					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%
Rough Coat		0	0	0	1 4%
DAY 14					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%
Rough Coat		0	0	0	1 4%
DAY 15					
No. Observed		25	25	25	25
Sacrificed Moribund		0	0	0	1 4%
Normal		25 100%	25 100%	25 100%	24 96%
DAY 16					
No. Observed		25	25	25	24
Normal		25 100%	25 100%	25 100%	24 100%
DAY 17					
No. Observed		25	25	25	24
Normal		25 100%	25 100%	25 100%	24 100%
DAY 18					
No. Observed		25	25	25	24
Normal		25 100%	25 100%	25 100%	24 100%
DAY 19					
No. Observed		25	25	25	24
Normal		25 100%	25 100%	25 100%	21 88%
Rough Coat		0	0	0	3 12%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) / GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 20					
	No. Observed	25	25	25	24
	Normal	25 100%	25 100%	25 100%	20 83%
	Hunched Posture	0	0	0	3 12%
	Rough Coat	0	0	0	4 17%
DAY 21					
	No. Observed	25	25	25	24
	Sacrificed Moribund	0	0	0	5 21%
	Normal	25 100%	25 100%	25 100%	18 75%
	Hunched Posture	0	0	0	3 12%
	Rough Coat	0	0	0	5 21%
DAY 22					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	18 95%
	Rough Coat	0	0	0	1 5%
DAY 23					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	15 79%
	Rough Coat	0	0	0	4 21%
DAY 24					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	15 79%
	Hunched Posture	0	0	0	2 11%
	Rough Coat	0	0	0	4 21%
DAY 25					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	16 84%
	Hunched Posture	0	0	0	1 5%
	Rough Coat	0	0	0	3 16%
DAY 26					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	17 89%
	Hunched Posture	0	0	0	1 5%
	Rough Coat	0	0	0	2 11%

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 27					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	14 74%
	Hunched Posture	0	0	0	1 5%
	Piloerection	0	0	0	3 16%
	Rough Coat	0	0	0	2 11%
DAY 28					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	17 89%
	Rough Coat	0	0	0	2 11%
DAY 29					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	16 84%
	Rough Coat	0	0	0	3 16%
DAY 30					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	16 84%
	Rough Coat	0	0	0	3 16%
DAY 31					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	16 84%
	Rough Coat	0	0	0	3 16%
DAY 32					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	15 79%
	Piloerection	0	0	0	1 5%
	Rough Coat	0	0	0	3 16%
DAY 33					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	14 74%
	Dark Material Around Nose	0	0	0	1 5%
	Piloerection	0	0	0	2 11%
	Rough Coat	0	0	0	2 11%
DAY 34					
	No. Observed	25	25	25	19
	Normal	25 100%	25 100%	25 100%	17 89%
	Rough Coat	0	0	0	2 11%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 35					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	15 79%
Piloerection		0	0	0	2 11%
Rough Coat		0	0	0	2 11%
DAY 36					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	15 79%
Piloerection		0	0	0	2 11%
Rough Coat		0	0	0	2 11%
DAY 37					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	15 79%
Piloerection		0	0	0	2 11%
Rough Coat		0	0	0	2 11%
DAY 38					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	15 79%
Piloerection		0	0	0	2 11%
Rough Coat		0	0	0	2 11%
DAY 39					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	18 95%
Rough Coat		0	0	0	1 5%
DAY 40					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	18 95%
Rough Coat		0	0	0	1 5%
DAY 41					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	18 95%
Rough Coat		0	0	0	1 5%

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 42					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	17 89%
Rough Coat		0	0	0	2 11%
DAY 43					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	17 89%
Rough Coat		0	0	0	2 11%
DAY 44					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	17 89%
Rough Coat		0	0	0	2 11%
DAY 45					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	17 89%
Rough Coat		0	0	0	2 11%
DAY 46					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	18 95%
Rough Coat		0	0	0	1 5%
DAY 47					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	18 95%
Rough Coat		0	0	0	1 5%
DAY 48					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 49					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 50					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 51					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 52					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 53					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 54					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 55					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 56					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 57					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 58					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	17 89%
Piloerection		0	0	0	2 11%
DAY 59					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%
DAY 60					
No. Observed		25	25	25	19
Normal		25 100%	25 100%	25 100%	19 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 197M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-M	0.3 2-M	1 3-M	3 4-M
DAY 61					
No. Observed		25	25	25	19
Scheduled Sacrifice		7 28%	11 44%	9 36%	5 26%
Normal		18 72%	14 56%	16 64%	14 74%
DAY 62					
No. Observed		18	14	16	14
Scheduled Sacrifice		8 44%	6 43%	9 56%	8 57%
Normal		10 56%	8 57%	7 44%	6 43%
DAY 63					
No. Observed		10	8	7	6
Scheduled Sacrifice		10 100%	8 100%	7 100%	6 100%

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
101	335	353	372	377	398	407	423	434	417	451	444	459
102	341	356	371	377	396	406	425	435	450	459	457	474
103	345	364	390	399	425	439	457	472	487	494	502	520
104	321	338	352	358	375	383	405	416	424	435	406	430
105	335	353	371	371	393	394	413	427	438	445	451	454
106	343	364	388	394	421	425	442	460	473	477	485	497
107	360	369	397	408	423	436	452	462	470	477	481	493
108	352	373	392	398	424	435	445	461	470	482	484	496
109	338	356	380	389	411	419	432	446	460	447	450	458
110	333	339	363	373	385	399	414	425	433	443	442	455
111	343	358	379	386	407	415	433	449	464	474	464	481
112	324	339	366	373	394	398	413	434	441	455	459	470
113	326	332	351	357	372	381	397	409	419	430	427	437
114	319	338	359	368	387	396	413	426	433	451	437	458
115	355	369	391	400	419	425	443	454	464	429	464	479
116	342	354	376	383	409	415	436	450	464	471	465	472
117	326	338	358	368	381	391	405	421	431	435	443	456
118	333	348	372	367	383	391	412	430	435	437	446	453
119	354	366	398	404	430	432	456	472	480	489	490	500
120	367	391	413	419	453	458	482	496	514	524	518	532
121	312	319	339	343	357	363	375	386	397	402	402	413
122	330	342	369	380	407	422	446	458	473	484	487	501
123	358	380	405	412	439	448	474	496	503	513	513	518
124	327	345	370	369	385	395	414	430	435	451	450	453
125	345	349	373	382	400	406	430	441	448	462	463	468
MEAN	339	353	376	382	403	411	429	444	453	461	461	473
S.D.	14.0	16.4	17.8	18.7	22.8	22.9	24.6	25.6	27.9	28.0	29.2	28.9
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	DAY 62	DAY 63
101	468	471	482	488	501	502	505	b	b
102	491	497	508	517	516	522	529	--	538
103	529	531	538	551	553	569	575	--	584
104	446	457	467	472	478	486	493	--	497
105	470	476	490	499	509	508	518	529	b
106	511	522	535	543	556	560	567	--	578
107	496	500	507	524	529	542	554	--	554
108	499	508	514	526	534	541	555	b	b
109	477	492	500	506	512	519	524	--	528
110	469	474	482	494	494	473	500	506	b
111	481	494	500	512	528	529	541	--	550
112	487	508	525	529	529	527	536	539	b
113	450	459	472	474	481	482	494	b	b
114	472	474	484	492	496	498	513	--	515
115	496	504	519	524	527	512	531	b	b
116	500	511	525	533	543	538	556	562	b
117	465	478	488	497	506	516	525	525	b
118	470	477	489	487	502	503	498	--	526
119	518	525	538	549	549	544	547	b	b
120	557	569	583	592	597	605	607	--	619
121	424	429	441	445	449	453	469	b	b
122	516	526	540	546	553	556	570	b	b
123	534	547	557	568	577	574	588	593	b
124	468	473	477	489	495	497	508	514	b
125	489	496	513	525	535	534	551	556	b
MEAN	487	496	507	515	522	524	534	541	549
S.D.	29.7	30.8	31.5	33.0	32.9	34.4	33.3	28.6	36.4
N	25	25	25	25	25	25	25	8	10

--: Data Unavailable b: Scheduled Sacrifice

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3(mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
151	360	370	396	409	434	442	465	480	497	506	513	522
152	334	340	358	362	378	384	402	407	414	425	418	427
153	316	331	347	357	371	379	398	406	411	424	429	436
154	346	362	388	399	428	437	462	476	491	505	506	516
155	336	360	378	388	409	418	436	446	460	474	470	479
156	324	335	355	359	379	388	400	411	416	423	424	430
157	326	339	360	361	383	390	408	416	425	427	443	449
158	349	357	385	391	412	426	447	459	476	487	487	495
159	329	344	366	376	399	410	425	439	452	466	468	481
160	326	337	359	361	378	388	405	418	428	442	452	455
161	344	359	390	397	420	427	446	463	472	490	494	503
162	342	361	382	390	405	415	432	444	456	467	470	481
163	333	345	373	378	402	409	422	435	446	453	460	466
164	340	355	380	390	410	419	434	448	461	468	470	482
165	339	353	375	384	405	415	437	443	462	468	474	483
166	341	358	381	393	417	429	451	461	471	486	490	507
167	318	332	355	360	375	374	385	396	406	414	423	430
168	333	353	382	393	413	424	447	464	478	488	488	499
169	353	358	387	391	419	421	441	457	468	477	479	490
170	320	331	354	359	377	386	403	417	428	437	439	451
171	371	377	409	415	441	449	467	479	494	507	513	521
172	329	335	358	368	396	404	415	427	438	449	455	462
173	356	375	401	409	426	435	452	462	480	491	497	498
174	356	373	401	403	428	442	463	474	486	496	496	506
175	345	352	374	382	400	413	429	442	450	465	463	471
MEAN	339	352	376	383	404	413	431	443	455	465	469	478
S.D.	13.9	14.2	17.0	18.0	20.4	21.5	23.8	25.0	27.6	28.7	28.2	29.1
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	DAY 62	DAY 63
151	541	550	562	567	575	588	567	599	b
152	445	450	460	469	469	477	487	b	b
153	449	457	463	464	474	478	491	--	496
154	532	537	549	564	572	585	600	b	b
155	495	499	509	521	534	532	542	550	b
156	440	449	462	473	478	486	495	b	b
157	461	470	480	486	495	504	505	--	510
158	510	518	526	522	530	543	558	--	562
159	500	499	506	507	527	524	537	b	b
160	470	476	483	491	495	500	502	b	b
161	518	526	536	543	552	560	565	--	576
162	491	503	507	538	522	526	540	b	b
163	479	484	493	505	512	520	520	b	b
164	492	503	517	527	527	530	535	538	b
165	496	503	511	523	532	531	539	544	b
166	524	524	534	548	545	541	557	b	b
167	442	449	454	461	468	474	474	482	b
168	514	523	537	545	557	562	564	568	b
169	501	511	513	517	528	529	545	b	b
170	461	466	474	484	493	499	502	--	505
171	538	545	563	572	583	592	596	--	612
172	472	481	489	504	505	514	519	--	530
173	517	522	530	537	545	548	569	b	b
174	518	524	532	536	552	544	549	--	568
175	483	496	507	514	522	528	538	b	b
MEAN	492	499	508	517	524	529	536	547	545
S.D.	30.6	30.3	31.6	32.2	33.0	33.2	33.2	38.6	40.9
N	25	25	25	25	25	25	25	6	8

--: Data Unavailable b: Scheduled Sacrifice

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
201	355	371	394	405	438	441	460	469	489	495	500	506
202	326	338	361	371	388	396	413	422	437	445	448	464
203	356	377	403	405	423	432	453	462	480	490	486	496
204	363	379	400	410	433	441	458	473	491	501	499	513
205	318	324	347	346	365	368	379	394	399	408	413	422
206	343	353	378	381	403	408	427	439	447	457	457	469
207	341	355	380	386	402	411	424	436	447	455	454	466
208	357	368	389	402	422	428	456	471	481	493	487	499
209	328	338	360	367	383	390	405	416	433	442	451	465
210	337	350	374	373	398	393	403	412	423	430	425	438
211	327	340	369	368	386	388	399	417	418	435	431	440
212	363	377	400	404	421	425	438	451	451	465	457	418
213	332	335	357	361	377	385	396	410	420	429	434	444
214	330	342	361	369	385	398	406	417	423	434	438	441
215	334	351	369	370	387	394	405	413	425	429	438	447
216	334	344	366	372	392	395	410	420	434	442	448	457
217	336	339	368	365	385	388	397	406	409	419	419	429
218	315	317	333	344	358	364	378	389	400	404	412	426
219	340	346	369	373	390	392	408	409	417	431	434	443
220	351	366	382	388	406	414	423	445	453	466	467	476
221	324	333	360	360	383	389	407	421	433	442	438	444
222	345	354	380	380	407	410	428	448	454	466	474	485
223	345	365	387	397	417	426	444	457	471	475	483	490
224	347	356	378	379	403	416	433	444	456	468	460	470
225	323	331	351	359	377	385	404	417	423	432	440	440
MEAN	339	350	373	377	397	403	418	430	441	450	452	460
S.D.	13.6	17.0	17.4	18.4	20.3	20.9	23.4	24.2	26.6	26.9	25.4	27.2
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1(mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	DAY 62	DAY 63
201	523	528	545	555	567	573	552	b	b
202	476	483	487	514	497	497	502	510	b
203	507	513	528	533	539	536	546	553	b
204	538	545	554	569	568	572	571	--	583
205	431	412	443	446	453	460	465	--	473
206	480	495	501	517	518	523	526	534	b
207	470	474	481	526	493	495	505	b	b
208	515	526	526	540	539	545	553	--	558
209	470	480	485	495	497	507	519	b	b
210	448	456	455	462	465	470	463	--	478
211	453	462	465	474	483	486	494	--	500
212	370	441	465	480	501	512	531	b	b
213	457	466	474	479	483	490	505	b	b
214	454	464	465	471	476	489	489	503	b
215	454	453	465	469	474	482	484	500	b
216	474	475	480	489	496	499	508	b	b
217	444	444	455	457	458	461	466	472	b
218	439	446	452	465	469	458	464	--	477
219	456	465	474	476	476	477	484	b	b
220	493	506	516	528	532	538	557	b	b
221	464	475	490	490	508	512	521	b	b
222	497	505	511	515	521	526	528	535	b
223	506	509	527	530	541	545	553	--	558
224	492	497	506	511	517	528	529	532	b
225	449	458	466	467	473	476	479	487	b
MEAN	470	479	489	498	502	506	512	514	518
S.D.	34.9	31.5	30.7	33.1	32.5	33.1	32.7	26.2	46.6
N	25	25	25	25	25	25	25	9	7

--: Data Unavailable b: Scheduled Sacrifice

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
251	323	340	360	363	374	380	391	403	409	409	383	357
252	319	329	345	345	294	249	d	d	d	d	d	d
253	333	345	367	366	385	379	390	399	403	406	400	403
254	327	342	357	360	374	377	388	393	396	409	406	405
255	345	359	379	377	391	388	408	411	408	422	408	412
256	343	360	374	372	386	393	383	376	358	349	363	387
257	335	347	370	356	359	354	319	d	d	d	d	d
258	346	361	385	384	402	399	404	414	404	395	359	349
259	311	320	337	333	349	348	357	355	357	365	342	333
260	354	362	382	382	390	380	366	351	316	303	321	365
261	334	339	361	357	367	357	315	d	d	d	d	d
262	323	337	352	352	359	362	365	380	381	384	373	343
263	341	353	373	372	390	390	400	408	412	421	401	366
264	350	358	373	373	379	352	303	d	d	d	d	d
265	328	336	355	354	368	367	371	378	372	383	375	379
266	360	383	400	404	413	423	433	436	441	450	407	385
267	329	336	361	361	357	312	266	d	d	d	d	d
268	372	385	402	403	423	420	431	431	422	386	350	323
269	333	342	356	358	377	381	397	405	422	428	430	431
270	340	350	372	361	356	354	378	371	374	381	339	321
271	355	376	391	387	405	416	426	442	451	461	451	470
272	345	353	372	366	383	383	381	379	349	322	333	365
273	325	337	354	353	360	351	307	d	d	d	d	d
274	337	347	370	367	381	381	397	409	411	405	360	318
275	357	369	383	385	392	387	360	330	309	302	288	316
MEAN	339	351	369	368	377	371	372	393	389	388	373	370
S.D.	14.4	16.2	16.0	16.8	25.4	35.6	42.9	29.6	38.6	44.5	40.2	41.8
N	25	25	25	25	25	25	24	19	19	19	19	19

--: Data Unavailable d: Sacrificed Moribund

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	DAY 62	DAY 63
251	325	327	369	403	412	430	433	--	439
252	d	d	d	d	d	d	d	d	d
253	417	428	443	451	456	459	461	--	470
254	415	426	445	453	466	473	473	--	493
255	426	435	457	460	453	454	455	b	b
256	395	412	405	387	368	384	409	421	b
257	d	d	d	d	d	d	d	d	d
258	380	406	434	467	442	445	420	438	b
259	356	365	360	366	327	306	340	--	361
260	394	403	396	413	367	353	381	b	b
261	d	d	d	d	d	d	d	d	d
262	318	316	359	391	410	418	428	443	b
263	335	341	373	410	442	446	449	--	430
264	d	d	d	d	d	d	d	d	d
265	399	408	417	426	425	432	433	437	b
266	396	425	447	466	437	499	513	b	b
267	d	d	d	d	d	d	d	d	d
268	315	308	358	399	438	451	490	491	b
269	441	455	451	448	455	449	438	456	b
270	295	328	380	385	409	426	430	--	435
271	473	481	493	500	494	496	510	b	b
272	387	400	422	429	414	382	367	369	b
273	d	d	d	d	d	d	d	d	d
274	350	386	421	438	448	448	410	b	b
275	365	396	425	440	438	433	414	413	b
MEAN	378	392	413	428	426	431	434	434	438
S.D.	47.2	48.8	39.0	34.7	39.2	47.1	44.8	35.2	44.8
N	19	19	19	19	19	19	19	8	6

--: Data Unavailable b: Scheduled Sacrifice d: Sacrificed Moribund

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
101	19	5	21	9	16	11	-17	34	-7	15	9
102	15	6	19	10	19	10	15	9	-2	17	17
103	26	9	26	14	18	15	15	7	8	18	9
104	14	6	17	8	22	11	8	11	-29	24	16
105	18	0	22	1	19	14	11	7	6	3	16
106	24	6	27	4	17	18	13	4	8	12	14
107	28	11	15	13	16	10	8	7	4	12	3
108	19	6	26	11	10	16	9	12	2	12	3
109	24	9	22	8	13	14	14	-13	3	8	19
110	24	10	12	14	15	11	8	10	-1	13	14
111	21	7	21	8	18	16	15	10	-10	17	0
112	27	7	21	4	15	21	7	14	4	11	17
113	19	6	15	9	16	12	10	11	-3	10	13
114	21	9	19	9	17	13	7	18	-14	21	14
115	22	9	19	6	18	11	10	-35	35	15	17
116	22	7	26	6	21	14	14	7	-6	7	28
117	20	10	13	10	14	16	10	4	8	13	9
118	24	-5	16	8	21	18	5	2	9	7	17
119	32	6	26	2	24	16	8	9	1	10	18
120	22	6	34	5	24	14	18	10	-6	14	25
121	20	4	14	6	12	11	11	5	D	11	11
122	27	11	27	15	24	12	15	11	3	14	15
123	25	7	27	9	26	22	7	10	0	5	16
124	25	-1	16	10	19	16	5	16	-1	3	15
125	24	9	18	6	24	11	7	14	1	5	21
MEAN	22	6	21	8	18	14	9	8	1	12	14
S.D.	4.1	3.8	5.5	3.6	4.2	3.3	6.5	11.8	10.9	5.3	6.4
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	TOTAL GAIN
101	3	11	6	13	1	3	152
102	6	11	9	-1	6	7	173
103	2	7	13	2	16	6	211
104	11	10	5	6	8	7	155
105	6	14	9	10	-1	10	165
106	11	13	8	13	4	7	203
107	4	7	17	5	13	12	185
108	9	6	12	8	7	14	182
109	15	8	6	6	7	5	168
110	5	8	12	0	-21	27	161
111	13	6	12	16	1	12	183
112	21	17	4	0	-2	9	197
113	9	13	2	7	1	12	162
114	2	10	8	4	2	15	175
115	8	15	5	3	-15	19	162
116	11	14	8	10	-5	18	202
117	13	10	9	9	10	9	187
118	7	12	-2	15	1	-5	150
119	7	13	11	0	-5	3	181
120	12	14	9	5	8	2	216
121	5	12	4	4	4	16	150
122	10	14	6	7	3	14	228
123	13	10	11	9	-3	14	208
124	5	4	12	6	2	11	163
125	7	17	12	10	-1	17	202
MEAN	9	11	8	7	2	11	181
S.D.	4.5	3.5	4.1	4.7	7.9	6.6	22.5
N	25	25	25	25	25	25	25

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3(mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
151	26	13	25	8	23	15	17	9	7	9	19
152	18	4	16	6	18	5	7	11	-7	9	18
153	16	10	14	8	19	8	5	13	5	7	13
154	26	11	29	9	25	14	15	14	1	10	16
155	18	10	21	9	18	10	14	14	-4	9	16
156	20	4	20	9	12	11	5	7	1	6	10
157	21	1	22	7	18	8	9	2	16	6	12
158	28	6	21	14	21	12	17	11	0	8	15
159	22	10	23	11	15	14	13	14	2	13	19
160	22	2	17	10	17	13	10	14	10	3	15
161	31	7	23	7	19	17	9	18	4	9	15
162	21	8	15	10	17	12	12	11	3	11	10
163	28	5	24	7	13	13	11	7	7	6	13
164	25	10	20	9	15	14	13	7	2	12	10
165	22	9	21	10	22	6	19	6	6	9	13
166	23	12	24	12	22	10	10	15	4	17	17
167	23	5	15	-1	11	11	10	8	9	7	12
168	29	11	20	11	23	17	14	10	0	11	15
169	29	4	28	2	20	16	11	9	2	11	11
170	23	5	18	9	17	14	11	9	2	12	10
171	32	6	26	8	18	12	15	13	6	8	17
172	23	10	28	8	11	12	11	11	6	7	10
173	26	8	17	9	17	10	18	11	6	1	19
174	28	2	25	14	21	11	12	10	0	10	12
175	22	8	18	13	16	13	8	15	-2	8	12
MEAN	24	7	21	9	18	12	12	11	3	9	14
S.D.	4.2	3.4	4.3	3.3	3.8	3.1	3.7	3.5	4.7	3.2	3.1
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3(mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	TOTAL GAIN
151	9	12	5	8	13	-21	197
152	5	10	9	0	8	10	147
153	8	6	1	10	4	13	160
154	5	12	15	8	13	15	238
155	4	10	12	13	-2	10	182
156	9	13	11	5	8	9	160
157	9	10	6	9	9	1	166
158	8	8	-4	8	13	15	201
159	-1	7	1	20	-3	13	193
160	6	7	8	4	5	2	165
161	8	10	7	9	8	5	206
162	12	4	31	-16	4	14	179
163	5	9	12	7	8	0	175
164	11	14	10	0	3	5	180
165	7	8	12	9	-1	8	186
166	0	10	14	-3	-4	16	199
167	7	5	7	7	6	0	142
168	9	14	8	12	5	2	211
169	10	2	4	11	1	16	187
170	5	8	10	9	6	3	171
171	7	18	9	11	9	4	219
172	9	8	15	1	9	5	184
173	5	8	7	8	3	21	194
174	6	8	4	16	-8	5	176
175	13	11	7	8	6	10	186
MEAN	7	9	9	7	5	7	184
S.D.	3.2	3.4	6.5	6.9	5.4	8.3	22.0
N	25	25	25	25	25	25	25

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
201	23	11	33	3	19	9	20	6	5	6	17
202	23	10	17	8	17	9	15	8	3	16	12
203	26	2	18	9	21	9	18	10	-4	10	11
204	21	10	23	8	17	15	18	10	-2	14	25
205	23	-1	19	3	11	15	5	9	5	9	9
206	25	3	22	5	19	12	8	10	0	12	11
207	25	6	16	9	13	12	11	8	-1	12	4
208	21	13	20	6	28	15	10	12	-6	12	16
209	22	7	16	7	15	11	17	9	9	14	5
210	24	-1	25	-5	10	9	11	7	-5	13	10
211	29	-1	18	2	11	18	1	17	-4	9	13
212	23	4	17	4	13	13	0	14	-8	-39	-48
213	22	4	16	8	11	14	10	9	5	10	13
214	19	8	16	13	8	11	6	11	4	3	13
215	18	1	17	7	11	8	12	4	9	9	7
216	22	6	20	3	15	10	14	8	6	9	17
217	29	-3	20	3	9	9	3	10	0	10	15
218	16	11	14	6	14	11	11	4	8	14	13
219	23	4	17	2	16	1	8	14	3	9	13
220	16	6	18	8	9	22	8	13	1	9	17
221	27	0	23	6	18	14	12	9	-4	6	20
222	26	0	27	3	18	20	6	12	8	11	12
223	22	10	20	9	18	13	14	4	8	7	16
224	22	1	24	13	17	11	12	12	-8	10	22
225	20	8	18	8	19	13	6	9	8	0	9
MEAN	23	5	20	6	15	12	10	10	2	8	11
S.D.	3.4	4.6	4.2	3.8	4.6	4.2	5.3	3.2	5.6	10.4	13.2
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	TOTAL GAIN
201	5	17	10	12	6	-21	181
202	7	4	27	-17	0	5	164
203	6	15	5	6	-3	10	169
204	7	9	15	-1	4	-1	192
205	-19	31	3	7	7	5	141
206	15	6	16	1	5	3	173
207	4	7	45	-33	2	10	150
208	11	0	14	-1	6	8	185
209	10	5	10	2	10	12	181
210	8	-1	7	3	5	-7	113
211	9	3	9	9	3	8	154
212	71	24	15	21	11	19	154
213	9	8	5	4	7	15	170
214	10	1	6	5	13	0	147
215	-1	12	4	5	8	2	133
216	1	5	9	7	3	9	164
217	0	11	2	1	3	5	127
218	7	6	13	4	-11	6	147
219	9	9	2	0	1	7	138
220	13	10	12	4	6	19	191
221	11	15	0	18	4	9	188
222	8	6	4	6	5	2	174
223	3	18	3	11	4	8	188
224	5	9	5	6	11	1	173
225	9	8	1	6	3	3	148
MEAN	9	10	10	3	5	5	162
S.D.	14.5	7.4	9.6	10.3	4.8	8.1	21.7
N	25	25	25	25	25	25	25

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
251	20	3	11	6	11	12	6	0	-26	-26	-32
252	16	0	-51	-45	d	d	d	d	d	d	d
253	22	-1	19	-6	11	9	4	3	-6	3	14
254	15	3	14	3	11	5	3	13	-3	-1	10
255	20	-2	14	-3	20	3	-3	14	-14	4	14
256	14	-2	14	7	-10	-7	-18	-9	14	24	8
257	23	-14	3	-5	-35	d	d	d	d	d	d
258	24	-1	18	-3	5	10	-10	-9	-36	-10	31
259	17	-4	16	-1	9	-2	2	8	-23	-9	23
260	20	0	8	-10	-14	-15	-35	-13	18	44	29
261	22	-4	10	-10	-42	d	d	d	d	d	d
262	15	0	7	3	3	15	1	3	-11	-30	-25
263	20	-1	18	0	10	8	4	9	-20	-35	-31
264	15	0	6	-27	-49	d	d	d	d	d	d
265	19	-1	14	-1	4	7	-6	11	-8	4	20
266	17	4	9	10	10	3	5	9	-43	-22	11
267	25	0	-4	-45	-46	d	d	d	d	d	d
268	17	1	20	-3	11	0	-9	-36	-36	-27	-8
269	14	2	19	4	16	8	17	6	2	1	10
270	22	-11	-5	-2	24	-7	3	7	-42	-18	-26
271	15	-4	18	11	10	16	9	10	-10	19	3
272	19	-6	17	0	-2	-2	-30	-27	11	32	22
273	17	-1	7	-9	-44	d	d	d	d	d	d
274	23	-3	14	0	16	12	2	-6	-45	-42	32
275	14	2	7	-5	-27	-30	-21	-7	-14	28	49
MEAN	19	-2	9	-5	-4	2	-4	-1	-15	-3	8
S.D.	3.4	4.1	14.2	14.2	23.3	11.3	13.5	13.6	19.3	24.5	23.0
N	25	25	25	25	24	19	19	19	19	19	19

--: Data Unavailable d: Sacrificed Moribund

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61	TOTAL GAIN
251	2	42	34	9	18	3	93
252	d	d	d	d	d	d	--
253	11	15	8	5	3	2	116
254	11	19	8	13	7	0	131
255	9	22	3	-7	1	1	96
256	17	-7	-18	-19	16	25	49
257	d	d	d	d	d	d	--
258	26	28	33	-25	3	-25	59
259	9	-5	6	-39	-21	34	20
260	9	-7	17	-46	-14	28	19
261	d	d	d	d	d	d	--
262	-2	43	32	19	8	10	91
263	6	32	37	32	4	3	96
264	d	d	d	d	d	d	--
265	9	9	9	-1	7	1	97
266	29	22	19	-29	62	14	130
267	d	d	d	d	d	d	--
268	-7	50	41	39	13	39	105
269	14	-4	-3	7	-6	-11	96
270	33	52	5	24	17	4	80
271	8	12	7	-6	2	14	134
272	13	22	7	-15	-32	-15	14
273	d	d	d	d	d	d	--
274	36	35	17	10	0	-38	63
275	31	29	15	-2	-5	-19	45
MEAN	14	22	15	-2	4	4	81
S.D.	12.0	18.7	15.2	23.1	18.9	19.9	37.9
N	19	19	19	19	19	19	19

--: Data Unavailable b: Scheduled Sacrifice d: Sacrificed Moribund

[a]Weight gains compared to the previous period

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
101	27.8	4.3	25.3	23.3	23.5	25.0	25.5	23.7	23.3	27.7	--	--
102	29.5	26.7	27.0	25.3	24.0	24.7	24.3	25.0	27.5	26.0	26.3	27.8
103	31.5	28.3	32.3	28.3	28.8	29.3	30.0	30.7	31.3	29.3	--	--
104	27.5	24.7	24.8	23.3	23.8	23.7	25.5	25.0	25.3	24.3	29.0	26.8
105	27.5	26.0	27.8	24.3	24.5	23.7	25.5	25.3	26.8	25.0	25.7	26.5
106	30.3	27.7	27.5	25.7	26.3	25.0	27.3	28.0	27.8	25.7	28.3	28.0
107	31.0	26.7	29.5	27.0	26.3	27.3	28.0	26.3	27.3	26.0	--	--
108	31.3	37.7	29.3	27.0	28.5	28.0	27.3	27.7	27.5	27.3	--	--
109	28.3	57.3	26.3	25.3	25.3	22.3	24.5	25.0	26.5	17.3	29.3	28.8
110	28.5	24.0	25.3	23.7	23.3	24.7	24.0	24.0	25.3	24.3	25.3	27.0
111	30.5	26.7	29.5	25.0	25.0	25.0	25.3	25.7	27.0	24.3	--	--
112	29.3	24.3	29.0	27.0	25.3	24.7	25.8	27.3	28.3	26.0	27.7	28.8
113	27.8	24.7	25.5	24.0	22.5	23.7	24.3	23.3	26.0	24.7	24.0	23.3
114	26.5	27.0	25.5	24.0	23.5	24.0	25.0	24.7	25.8	25.0	26.7	26.0
115	32.3	25.3	27.8	26.3	27.0	25.7	27.5	27.3	28.0	19.7	28.3	28.8
116	29.5	24.7	26.5	25.3	27.3	26.0	25.8	27.3	28.0	25.3	26.3	29.0
117	27.8	26.7	28.3	32.0	22.5	24.3	25.0	25.0	25.8	23.7	27.0	25.5
118	29.3	27.3	27.8	25.3	24.8	24.7	26.3	27.0	27.5	23.7	25.3	28.3
119	31.0	27.3	30.8	27.7	26.0	26.7	28.5	26.7	27.8	26.7	27.7	9.8
120	32.5	29.0	32.0	28.0	30.3	27.7	29.5	29.3	31.8	27.7	30.3	31.3
121	28.8	24.3	26.5	25.0	25.8	22.3	25.8	23.3	24.8	21.3	24.0	24.5
122	28.5	25.0	26.8	24.7	25.0	27.0	27.5	26.3	29.3	26.0	27.7	28.3
123	31.8	28.7	29.0	27.3	28.3	28.0	30.3	30.3	30.0	28.0	27.0	28.3
124	31.5	26.7	31.0	24.7	24.3	24.7	28.8	27.3	30.3	27.0	28.7	28.8
125	30.5	23.0	26.8	25.0	23.0	25.0	26.5	26.0	26.8	26.7	26.7	27.5
MEAN	29.6	27.0	27.9	25.8	25.4	25.3	26.6	26.3	27.4	25.1	27.1	26.7
S.D.	1.70	8.22	2.13	1.95	2.08	1.78	1.84	1.99	2.00	2.64	1.69	4.35
N	25	25	25	25	25	25	25	25	25	25	20	20

--: Data Unavailable

[a] Calculated daily food consumption for successive period intervals

[b] Baseline is day -7

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61
101	--	--	24.3	28.3	24.0	26.5
102	25.3	27.3	26.3	25.8	24.3	27.0
103	--	--	--	31.0	28.3	30.3
104	25.7	26.0	24.7	26.3	23.3	25.3
105	26.0	26.8	26.7	28.5	23.7	28.3
106	28.7	29.5	29.3	30.5	27.7	29.0
107	27.3	28.0	29.0	29.3	28.7	31.5
108	27.7	27.5	27.0	28.5	27.0	29.5
109	27.3	27.0	25.3	27.8	24.3	25.8
110	24.3	25.8	25.7	25.5	22.3	24.8
111	28.7	27.8	27.7	30.5	26.3	28.8
112	29.3	31.8	26.7	29.3	25.7	29.3
113	25.3	26.0	25.0	25.0	23.7	28.0
114	25.7	26.5	25.3	26.3	24.0	28.0
115	28.0	27.0	28.7	26.5	22.7	25.0
116	29.0	30.0	28.7	29.5	25.3	28.5
117	27.3	25.8	26.3	29.3	25.7	28.5
118	26.7	28.0	23.3	29.3	25.7	27.0
119	28.0	31.8	27.0	26.8	22.3	24.0
120	32.0	32.3	30.3	31.5	29.0	31.0
121	25.0	24.0	24.3	24.5	23.7	29.0
122	28.0	29.0	27.7	30.0	27.0	28.5
123	30.7	29.8	29.0	29.5	25.7	28.8
124	27.3	29.5	27.0	30.3	25.7	30.0
125	27.3	27.8	28.0	29.3	26.7	28.8
MEAN	27.4	28.0	26.8	28.4	25.3	28.0
S.D.	1.85	2.13	1.83	1.99	1.95	1.95
N	23	23	24	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
151	30.5	26.3	29.3	27.0	26.0	26.3	28.0	27.0	29.5	27.0	28.7	30.0
152	29.5	24.3	27.0	25.3	22.5	22.7	24.0	22.3	22.3	22.7	--	26.0
153	26.5	24.7	23.8	24.7	21.5	24.0	25.0	22.7	23.8	23.7	--	25.5
154	30.3	25.7	27.0	27.7	28.5	26.3	29.0	27.3	29.5	26.7	28.3	29.0
155	29.3	27.7	28.8	27.0	25.0	26.0	26.5	26.3	28.5	26.3	29.0	28.0
156	27.3	24.3	26.0	24.3	22.0	23.7	24.8	23.0	24.0	23.3	23.7	23.3
157	29.0	25.7	25.3	23.0	23.5	23.3	24.5	24.0	25.5	22.0	26.7	25.5
158	29.3	25.3	29.0	27.0	26.0	29.3	28.8	28.3	29.8	28.7	--	--
159	26.5	32.3	31.5	24.0	25.3	25.3	25.8	25.3	28.8	25.0	28.3	30.8
160	27.5	24.3	25.8	23.3	23.8	24.0	25.0	24.0	25.5	24.3	--	27.0
161	27.8	26.0	30.0	27.3	26.5	26.3	27.3	26.7	28.8	27.3	26.7	29.3
162	34.0	27.7	28.0	28.0	26.0	25.3	26.5	25.0	27.5	25.3	26.7	27.0
163	29.5	24.3	26.8	25.7	26.0	26.3	25.5	24.7	26.5	24.3	25.3	26.5
164	29.0	25.3	26.8	25.3	25.8	25.3	24.8	24.3	27.5	24.7	27.3	26.5
165	31.3	26.3	33.0	25.7	26.5	26.7	28.3	26.3	30.0	26.7	28.3	29.8
166	29.3	28.3	30.0	27.3	27.8	27.7	27.8	27.3	29.5	28.0	29.7	29.5
167	27.0	24.7	26.0	24.7	23.0	21.7	22.5	20.7	24.0	22.7	24.0	24.0
168	29.5	3.7	27.0	27.3	25.8	27.0	27.0	27.0	28.3	30.3	27.3	27.3
169	29.5	25.3	26.8	25.0	27.0	25.3	28.5	27.0	27.5	26.0	27.3	27.8
170	27.8	23.7	27.3	23.7	24.0	24.0	26.0	25.7	27.8	24.3	28.0	28.5
171	31.3	29.0	31.3	27.3	28.0	27.7	28.8	26.3	28.5	27.3	28.3	28.8
172	26.8	22.7	24.5	24.7	25.3	24.0	24.5	23.7	26.0	24.0	24.3	25.5
173	31.0	26.7	30.0	27.7	26.5	27.7	28.5	25.0	29.0	26.7	26.7	28.5
174	30.0	30.0	28.8	27.0	27.8	28.3	30.0	29.3	30.3	28.3	30.3	29.5
175	31.5	24.7	27.5	24.7	25.0	26.7	26.8	26.3	27.3	25.7	25.7	28.5
MEAN	29.2	25.2	27.9	25.8	25.4	25.6	26.6	25.4	27.4	25.7	27.2	27.6
S.D.	1.83	4.96	2.25	1.54	1.88	1.87	1.91	2.01	2.20	2.08	1.80	1.95
N	25	25	25	25	25	25	25	25	25	25	21	24

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 2-M SEX: MALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61
151	28.7	29.8	28.7	29.8	28.3	28.5
152	28.0	26.0	26.3	25.8	25.3	27.8
153	25.0	23.5	17.7	26.0	23.3	26.0
154	25.7	27.0	29.0	30.5	27.7	29.8
155	25.7	29.3	26.7	29.3	26.7	28.5
156	23.0	24.3	24.3	25.0	26.3	25.3
157	25.7	25.8	24.7	25.8	24.3	25.0
158	--	--	--	28.8	29.0	30.8
159	26.7	29.0	26.0	28.3	25.7	29.3
160	25.7	27.0	24.7	26.8	24.3	25.3
161	29.0	29.8	27.3	29.5	26.7	29.0
162	26.0	27.0	25.7	27.8	26.0	27.5
163	25.3	27.3	26.3	27.8	24.3	26.8
164	27.0	28.0	24.7	26.5	23.7	25.5
165	29.3	30.5	28.3	29.8	26.0	27.3
166	28.3	28.5	27.0	29.0	26.7	28.5
167	24.3	25.0	22.7	24.8	23.3	23.3
168	27.7	28.8	28.0	28.5	27.0	27.0
169	26.7	32.0	25.7	27.3	24.0	27.8
170	26.7	27.0	26.3	28.0	25.3	27.5
171	29.3	32.3	29.0	6.5	29.3	30.8
172	25.3	26.0	25.7	28.0	25.0	26.5
173	27.3	28.8	27.0	28.5	25.0	28.8
174	26.0	29.5	30.0	30.5	26.7	28.8
175	29.7	31.3	27.7	29.3	26.3	28.5
MEAN	26.8	28.1	26.2	27.1	25.8	27.6
S.D.	1.73	2.33	2.51	4.59	1.66	1.84
N	24	24	24	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
201	31.0	29.3	28.8	25.0	26.3	26.0	27.5	27.7	28.8	26.7	28.0	27.3
202	28.5	26.3	38.0	26.3	24.3	25.3	25.8	26.0	27.8	26.7	27.7	26.5
203	29.0	27.3	30.5	25.3	25.8	26.3	28.0	26.3	29.3	25.7	27.0	28.5
204	30.3	28.7	26.5	26.3	24.8	25.7	26.5	26.3	28.8	27.0	28.7	30.3
205	30.0	24.0	35.0	24.3	24.3	24.7	25.5	25.7	26.3	24.3	25.7	26.5
206	33.8	27.0	32.0	26.7	26.0	25.0	25.5	24.7	26.3	24.0	25.7	26.3
207	29.5	25.7	28.5	26.3	25.3	25.7	26.8	25.3	27.5	25.0	27.7	26.0
208	32.8	28.0	31.3	27.0	27.3	26.0	31.8	27.3	30.0	27.7	29.3	29.8
209	28.0	26.7	26.8	24.3	25.3	26.0	25.8	24.7	27.8	27.0	--	--
210	26.5	25.7	27.3	24.3	25.3	22.7	22.3	23.0	23.5	26.0	25.7	25.3
211	27.0	24.0	26.5	24.7	24.3	24.0	25.3	23.7	25.0	25.0	27.0	25.3
212	32.0	29.0	29.3	26.3	25.0	24.3	24.5	26.7	27.3	25.7	17.0	5.8
213	26.8	21.7	23.8	23.3	22.0	23.7	23.3	23.7	26.3	23.3	25.7	25.8
214	29.3	27.3	27.5	27.0	25.0	27.0	26.3	24.7	26.3	24.7	25.3	26.8
215	26.8	26.7	25.3	25.3	23.3	24.0	24.3	23.0	26.5	23.7	--	--
216	29.0	25.3	26.3	25.3	24.0	24.3	25.5	24.3	27.3	25.0	28.0	27.5
217	26.8	23.0	26.0	23.0	22.8	22.3	24.5	23.3	24.0	23.3	24.7	25.8
218	27.3	22.0	21.5	24.7	25.3	22.0	21.8	24.0	26.5	23.0	27.3	27.0
219	27.0	26.0	24.8	24.0	23.8	22.3	23.8	22.7	24.8	24.3	25.0	26.5
220	28.0	25.3	24.3	24.3	23.5	23.7	23.0	25.7	26.5	25.3	26.0	28.3
221	28.0	25.7	28.3	25.0	24.8	24.3	27.3	27.7	28.0	25.7	25.3	28.5
222	33.5	26.0	29.8	26.3	34.8	25.7	27.5	28.3	33.5	28.0	28.3	30.0
223	28.5	27.3	28.3	25.7	26.0	25.7	27.8	26.7	29.3	26.3	26.7	27.8
224	28.5	25.3	24.3	26.0	25.3	25.7	26.0	26.3	27.5	26.0	26.7	29.3
225	26.8	25.3	23.5	--	22.8	23.3	24.3	24.0	24.5	25.3	--	23.5
MEAN	29.0	25.9	27.8	25.3	25.1	24.6	25.6	25.3	27.2	25.4	26.3	26.3
S.D.	2.18	1.96	3.68	1.13	2.36	1.39	2.13	1.63	2.14	1.37	2.44	4.77
N	25	25	25	24	25	25	25	25	25	25	22	23

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 3-M SEX: MALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61
201	27.0	30.5	28.3	30.3	28.3	27.0
202	26.3	32.0	25.3	25.0	24.0	25.8
203	27.3	30.3	27.7	27.8	24.7	26.3
204	29.0	30.0	27.7	29.3	27.7	28.0
205	19.7	27.0	27.7	28.3	25.3	28.0
206	27.7	30.3	25.7	27.5	26.0	27.5
207	25.7	28.8	26.3	26.8	25.0	29.3
208	29.7	29.8	27.7	27.5	26.0	29.0
209	--	--	--	29.5	28.3	29.3
210	24.3	24.3	23.7	16.5	--	13.3
211	26.0	25.3	26.3	27.3	24.3	26.5
212	27.0	36.8	34.3	34.3	30.7	33.3
213	25.0	26.3	24.0	26.0	23.7	26.3
214	26.7	28.8	26.0	27.3	26.3	28.0
215	--	28.8	23.0	27.0	25.0	24.5
216	27.0	28.3	26.0	27.8	24.7	28.0
217	24.7	25.5	23.3	25.0	23.0	24.3
218	25.3	27.0	25.7	26.3	21.7	24.0
219	25.0	26.5	23.3	24.5	23.0	24.8
220	28.7	28.3	28.0	28.5	27.0	26.5
221	27.7	29.3	25.7	30.5	26.3	28.5
222	29.7	29.5	27.3	28.8	27.3	28.5
223	27.7	28.8	27.3	29.3	26.3	29.5
224	26.7	28.8	26.0	28.8	27.3	27.0
225	25.3	25.8	23.7	26.3	25.3	25.0
MEAN	26.5	28.6	26.3	27.4	25.7	26.7
S.D.	2.13	2.60	2.38	3.08	2.01	3.47
N	23	24	24	25	24	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
251	27.5	25.0	24.0	22.7	20.8	21.3	20.3	22.7	24.0	20.3	9.7	5.5
252	26.0	24.3	24.8	23.0	6.5	0.7	d	d	d	d	d	d
253	27.5	24.0	28.0	21.7	22.5	19.0	22.0	21.3	21.3	21.7	22.0	23.5
254	25.5	26.0	24.3	21.3	18.8	19.0	19.8	30.0	21.3	20.7	22.0	23.3
255	30.3	26.7	27.5	20.3	21.5	21.7	24.5	23.3	24.3	23.3	22.0	23.3
256	29.0	25.7	23.5	20.7	21.3	22.7	17.8	15.7	15.8	8.3	22.7	22.3
257	28.5	26.3	25.0	21.7	18.0	16.3	9.8	d	d	d	d	d
258	31.3	29.0	29.0	23.3	23.5	23.0	21.5	24.3	22.0	18.0	10.0	21.5
259	27.0	23.3	24.0	18.0	20.5	20.0	21.5	20.0	22.0	20.3	15.0	20.5
260	29.8	26.7	28.3	22.7	21.0	19.0	15.5	13.3	13.3	9.3	--	--
261	29.8	26.3	27.0	22.3	20.3	18.3	7.0	d	d	d	d	d
262	30.0	27.3	25.5	22.0	19.8	21.0	20.3	22.0	23.8	20.3	8.7	9.8
263	27.8	25.0	25.3	21.7	22.3	19.0	23.0	22.3	24.5	22.0	8.7	7.5
264	30.3	26.3	23.5	21.3	20.0	12.3	3.3	d	d	d	d	d
265	26.8	21.0	24.8	21.3	19.8	20.7	20.8	22.7	21.5	20.7	21.7	23.3
266	30.0	29.3	26.5	24.0	21.0	23.0	23.0	20.3	24.5	22.0	8.3	12.8
267	28.0	27.0	29.5	25.7	18.8	3.0	0.8	d	d	d	d	d
268	32.5	31.3	33.5	25.0	29.0	22.0	23.0	22.7	19.8	7.3	--	--
269	27.3	26.0	29.3	22.0	22.8	24.0	26.5	24.7	30.0	24.0	24.0	26.3
270	28.3	25.7	28.0	19.3	15.0	18.3	19.5	15.7	23.0	18.7	5.7	8.3
271	31.5	29.0	27.5	19.0	21.5	23.0	22.0	27.3	26.8	24.3	26.0	22.3
272	28.3	25.3	27.3	20.7	21.8	21.0	20.8	19.3	12.0	3.7	24.3	27.0
273	27.8	25.0	30.5	19.3	19.0	14.7	6.8	d	d	d	d	d
274	27.8	24.7	24.3	21.0	20.8	24.0	20.8	25.0	23.5	18.3	3.7	16.0
275	32.0	27.3	27.3	21.3	19.8	20.3	13.0	5.7	13.8	7.0	16.7	36.3
MEAN	28.8	26.1	26.7	21.7	20.2	18.7	17.6	21.0	21.4	17.4	16.0	19.4
S.D.	1.86	2.11	2.49	1.79	3.76	5.80	7.04	5.44	4.69	6.60	7.58	8.22
N	25	25	25	25	25	25	24	19	19	19	17	17

--: Data Unavailable d: Sacrificed Moribund

[a]Calculated daily food corsumption for successive period intervals

[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197M GROUP: 4-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	DAY 57	DAY 61
251	12.0	22.3	31.0	26.5	27.7	24.5
252	d	d	d	d	d	d
253	24.0	24.3	22.7	24.8	23.0	23.3
254	25.3	25.8	24.7	26.8	25.3	26.3
255	24.0	26.5	24.0	26.0	22.0	22.0
256	23.3	19.8	12.7	11.0	15.0	24.8
257	d	d	d	d	d	d
258	28.0	28.0	26.7	25.3	23.3	21.5
259	20.3	18.3	18.7	9.5	7.0	20.3
260	--	--	--	12.5	8.3	19.5
261	d	d	d	d	d	d
262	12.0	24.8	30.7	30.0	25.0	25.5
263	13.0	21.3	31.7	30.5	23.3	24.3
264	d	d	d	d	d	d
265	25.0	23.8	23.7	24.3	23.7	23.5
266	25.3	30.3	27.3	26.5	28.7	26.0
267	d	d	d	d	d	d
268	--	--	--	36.3	28.0	35.5
269	26.3	25.0	20.3	25.3	20.3	22.5
270	17.7	26.8	25.0	25.3	22.0	25.8
271	30.0	27.8	27.3	28.0	25.0	28.5
272	25.7	25.3	23.0	20.0	7.3	9.8
273	d	d	d	d	d	d
274	28.7	30.5	27.7	26.3	21.7	14.8
275	31.0	33.3	30.3	26.8	21.3	16.5
MEAN	23.0	25.5	25.1	24.3	20.9	22.9
S.D.	6.03	3.88	4.92	6.73	6.71	5.45
N	17	17	17	19	19	19

--: Data Unavailable d: Sacrificed Moribund

[a]Calculated daily food consumption for successive period intervals

DRAFT

APPENDIX C

SPERM ASSESSMENT REPORT

DRAFT

MALE REPRODUCTIVE ASSESSMENT REPORT

FOR

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

UIC/TRL STUDY NUMBER: 197

PREPARED FOR:

TOXICOLOGY RESEARCH LABORATORY (TRL)
UNIVERSITY OF CHICAGO AT ILLINOIS (UIC)
DEPARTMENT OF PHARMACOLOGY
1940 W. TAYLOR ST
CHICAGO, IL 60612-7353

15 Worman's Mill Court, Suite I • Frederick, Maryland 21701 • (301) 663-1644 • (301) 663-8994 FAX

DRAFT

Draft Report
Study No.: TRL 197

TABLE OF CONTENTS

Draft Report
Study No.: TRL 197

INDEX OF TABLES AND APPENDICES

DRAFT

Male Reproductive Assessment Report

Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

UIC/TRL Study Number: 197

QUALITY ASSURANCE STATEMENT

This male reproductive assessment project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration. The male reproductive assessment narrative report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

Date of Inspection	Phase Inspected	Date Findings Reported to Management/ Study Teratologist
02/09/96	Sperm Count Sample Prep	02/13/96
03/06-08/96	Individual Animal Data (Raw Data)	03/08/96
03/06-08/96	Individual Animal Data (Data Entry)	03/08/96
03/06-08/96	Draft Male Reproductive Assessment Report	03/08/96
04/02/96	Second Draft Male Reproductive Assessment Report	04/02/96

Sharon E. Abel
Quality Assurance Division

April 2, 1996
Date

15 Worman's Mill Court, Suite I • Frederick, Maryland 21701 • (301) 663-1644 • (301) 663-8994 FAX

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

II. MATERIALS AND METHODS

A. Gross Necropsy

At study termination, the surviving male rats were euthanized by carbon dioxide asphyxiation. For all animals, the abdominal, thoracic and pelvic cavities were opened and the organs examined. Any abnormalities were recorded. Both testes were retained in Bouins's Fixative and the left epididymis, both seminal vesicles, the prostate gland and gross lesions were saved in 10% neutral buffered formalin for possible future histopathological examination.

B. Organ Weights

The testes, epididymides, seminal vesicles and prostate were excised, trimmed and weighed. The brain was also weighed to provide relative organ weight comparisons. Paired organs with observable differences in size were weighed separately.

C. Sperm Sample Collection

For motility assessment, the right vas deferens was removed and immediately placed in a petri dish containing 10 ml of a solution consisting of 1% Bovine Serum Albumin dissolved in Phosphate Buffered Saline. The solution was prewarmed to a temperature of approximately 38°C. A minimum 3 minute period was allowed for the sperm to swim out.

The right epididymis was weighed and placed on dry ice. The frozen epididymides were transferred to Pathology Associates Int., Frederick, MD. and stored frozen at -70°C or lower until evaluated for total sperm count and morphology.

D. Sperm Motility Evaluation

Following the swim out period, a sperm sample was obtained using a 100 μm deep cannula. The cannula was immediately loaded into the prewarmed stage of the Hamilton Thorne IVOS automated sperm analyzer. Five fields were automatically selected by the analyzer and each motion image was recorded and stored on an optical disk. The images were subsequently analyzed and the percent motility determined for each animal.

E. Total Sperm Count Determination

Each frozen epididymis was removed from the freezer, thawed and the caudal section was trimmed and weighed. The cauda epididymis was homogenized and the suspension was transferred to a plastic, conical tube and vortexed. A 100 μl sample was transferred to a vial containing a fluorescent dye which uniquely stains the head of the sperm. A sample of the stained sperm was placed into a 20 μm deep glass slide which was loaded into the analyzer. Twenty fields were automatically selected by the analyzer for each animal and total sperm counts determined. The counts were reported adjusted for caudal epididymal weight.

F. Sperm Morphology

Two Eosin stained slides were prepared from the minced caudal epididymal samples obtained from each animal. The slides were evaluated and a minimum of 200 sperm cells/animal were examined for morphological development.

G. Statistical Analyses

The means and standard deviations for the organ/brain weight ratios, sperm motility, total sperm count data and the percentage of morphologically abnormal sperm were calculated. The organ weight data were analyzed by one-way analysis of variance (ANOVA). If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons of the each treated group to the vehicle control group.

Sperm motility, total count and sperm morphology data were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ($p \leq 0.05$), the Wilcoxon (Mann-Whitney U) test was used for pair-wise comparisons of each treated group to the vehicle control group.

Statistical analysis were performed using an IBM™ compatible computer with SAS computer programs (SAS/STAT User's Guide, 1989).

DRAFT

III. RESULTS

A. Gross Necropsy Observations

Table 1 (Summary Data)
Appendix A (Individual Data)

No treatment-related gross lesions were observed. Incidental findings relateed to the lungs occurred in the control, 0.3 and 3.0 mg base/kg/day groups. Observations of testes, epididymis and/or seminal vesicles small in size were noted for a 3 males at the 3.0 mg base/kg/day level. For the epididymis and seminal vesicles, this observation correlated with reduced group mean organ weights.

B. Organ Weight Data

Table 2 (Summary Data)
Appendicies B and C (Individual Data)

Statistically significant reductions in relative epididymis, seminal vesicle and prostate weights occurred at the 3.0 mg base/kg/day level. Testes weights were comparable between study groups.

C. Sperm Motility

Table 3 (Summary Data)
Appendix D (Individual Data)

No apparent treatment-related effects were observed for the sperm motility data. Group mean values were comparable between the study groups, ranging from 94.48% in the control group to 98.33% in the 3.0 mg base/kg/day group. Animal 113 in the 0 mg base/kg/day group had 0% motility; tails only were present.

D. Total Sperm Count

Table 3 (Summary Data)
Appendix D (Individual Data)

The number of sperm/gram of cauda epididymis was comparable between the study groups. Mean values ranged from 835.6 to 893.6 million sperm/gram. No treatment-related differences were observed.

DRAFT

E. Sperm Morphology

Table 3 (Summary Data)
Appendix E (Individual Data)

A low incidence of head/tail abnormalities was observed for animals in all treatment group data. No treatment related differences were observed.

IV. DISCUSSION AND CONCLUSIONS

Oral administration of WR242511 Tartrate did not produce internal gross lesions in males. Statistically significant reductions in group mean epididymis, prostate and seminal vesicle weights relative to brain weight were observed in the 3.0 mg base/kg/day group. The changes in organs weights did not affect other male reproductive parameters including mean percent motility, total sperm count and sperm morphology. The no-effect level for male reproductive toxicity was established at 1.0 mg base/kg/day.

_____ Date: _____

Michael D. Mercieca, B.S.
Reproductive Toxicologist

V. REFERENCES

SAS Institute Inc., SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2 Cary, NC:SAS Institute Inc., 1989. Vol. 2 p. 201-244 and p. 1195-1210.

TABLE 1

STUDY NO.: TRL 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR-242511 TARTRATE IN RATS

SUMMARY OF GROSS NECROPSY OBSERVATIONS

GROUP:	1	2	3	4
DOSE LEVEL (MG/KG/DAY):	0	0.3	1.0	3.0
NUMBER OF MALES NECROPSIED	25	25	25	19
NO ABNORMALITIES DETECTED	23	24	25	14
TESTES				
-FAT NODULE, YELLOW, NECROTIC	1	0	0	0
-SMALL, RIGHT	0	0	0	1
LUNGS				
-MULTIPLE RED FOCI, ALL LOBES	1	1	0	0
-MULTIPLE WHITE FOCI, ALL LOBES	0	0	0	2
-MOTTLED WHITE, ALL LOBES	0	0	0	1
SEMINAL VESICLE				
-SMALL, LEFT	0	0	0	1
-SMALL, BILATERAL	0	0	0	1
EPIDIDYMIS				
-SMALL, RIGHT	0	0	0	1

DRAFT

DRAFT

TABLE 2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

SUMMARY OF ORGAN/BRAIN WEIGHT
RATIOS

Group Level (MG BASE/KG/DAY)		1 0	2 0.3	3 1.0	4 3.0
EPIDIDYMIS	MEAN	0.64	0.65	0.66	0.60*
	SD	0.06	0.04	0.05	0.06
	N	25	25	25	19
SEMINAL VESICLES	MEAN	0.87	0.93	0.85	0.66*
	SD	0.16	0.21	0.16	0.14
	N	25	25	25	19
PROSTATE	MEAN	0.49	0.50	0.46	0.35*
	SD	0.12	0.08	0.07	0.08
	N	25	25	25	19
TESTES	MEAN	1.62	1.65	1.64	1.62
	SD	0.14	0.09	0.16	0.20
	N	25	25	25	19

* SIGNIFICANTLY DIFFERENT FROM CONTROL ($p \leq 0.05$).

TABLE 3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

SUMMARY OF SPERM ANALYSIS PARAMETERS

PERCENT MOTILITY

Group Level	(MG BASE/KG/DAY)	1 0	2 0.3	3 1.0	4 3.0
	Mean	94.48	97.92	98.92	98.33
	SD	19.87	2.60	1.04	1.46
	N	25	25	25	18

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

SPERM DENSITY (MILLION SPERM/GRAM)

Group Level	(MG BASE/KG/DAY)	1 0	2 0.3	3 1.0	4 3.0
	Mean	876.32	893.56	890.87	835.56
	SD	404.73	352.10	360.81	419.95
	N	25	25	25	19

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

SPERM MORPHOLOGY DATA (PERCENT ABNORMAL)

Group Level	(MG BASE/KG/DAY)	1 0	2 0.3	3 1.0	4 3.0
	Mean	1.03	0.86	1.13	0.81
	SD	1.16	1.10	2.21	0.95
	N	25	25	25	19

MEAN AND STANDARD DEVIATIONS WERE CALCULATED USING THE TOTAL NUMBER OF ABNORMAL SPERM AS A PERCENTAGE OF THE NUMBER SPERM EXAMINED.
NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

APPENDIX A

STUDY NO.: TRL 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY VEHICLE

ANIMAL#	ORGAN	OBSERVATION
101	TESTES	FAT NODULE, YELLOW, NECROTIC
102		NO ABNORMALITIES DETECTED
103		NO ABNORMALITIES DETECTED
104		NO ABNORMALITIES DETECTED
105		NO ABNORMALITIES DETECTED
106		NO ABNORMALITIES DETECTED
107		NO ABNORMALITIES DETECTED
108		NO ABNORMALITIES DETECTED
109		NO ABNORMALITIES DETECTED
110		NO ABNORMALITIES DETECTED
111		NO ABNORMALITIES DETECTED
112		NO ABNORMALITIES DETECTED
113		NO ABNORMALITIES DETECTED
114	LUNGS	RED/MULTIPLE FOCI, ALL LOBES
115		NO ABNORMALITIES DETECTED
116		NO ABNORMALITIES DETECTED
117		NO ABNORMALITIES DETECTED
118		NO ABNORMALITIES DETECTED
119		NO ABNORMALITIES DETECTED
120		NO ABNORMALITIES DETECTED
121		NO ABNORMALITIES DETECTED
122		NO ABNORMALITIES DETECTED
123		NO ABNORMALITIES DETECTED
124		NO ABNORMALITIES DETECTED
125		NO ABNORMALITIES DETECTED

DRAFT

APPENDIX A

STUDY NO.: TRL 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 0.3 MG BASE/KG/DAY (WR242511)

ANIMAL#	ORGAN	OBSERVATION
151		NO ABNORMALITIES DETECTED
152		NO ABNORMALITIES DETECTED
153		NO ABNORMALITIES DETECTED
154	LUNGS	MULTIPLE/RED FOCI, ALL LOBES
155		NO ABNORMALITIES DETECTED
156		NO ABNORMALITIES DETECTED
157		NO ABMORMALITIES DETECTED
158		NO ABNORMALITIES DETECTED
159		NO ABNORMALITIES DETECTED
160		NO ABNORMALITIES DETECTED
161		NO ABNORMALITIES DETECTED
162		NO ABNORMALITIES DETECTED
163		NO ABNORMALITIES DETECTED
164		NO ABNORMALITIES DETECTED
165		NO ABNORMALITIES DETECTED
166		NO ABNORMALITIES DETECTED
167		NO ABNORMALITIES DETECTED
168		NO ABNORMALITIES DETECTED
169		NO ABNORMALITIES DETECTED
170		NO ABNORMALITIES DETECTED
171		NO ABNORMALITIES DETECTED
172		NO ABNORMALITIES DETECTED
173		NO ABNORMALITIES DETECTED
174		NO ABNORMALITIES DETECTED
175		NO ABNORMALITIES DETECTED

DRAFT

APPENDIX A

STUDY NO.: TRL 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 1.0 MG BASE/KG/DAY (WR242511)

ANIMAL#	ORGAN	OBSERVATION
201		NO ABNORMALITIES DETECTED
202		NO ABNORMALITIES DETECTED
203		NO ABNORMALITIES DETECTED
204		NO ABNORMALITIES DETECTED
205		NO ABNORMALITIES DETECTED
206		NO ABNORMALITIES DETECTED
207		NO ABMORMALITIES DETECTED
208		NO ABNORMALITIES DETECTED
209		NO ABNORMALITIES DETECTED
210		NO ABNORMALITIES DETECTED
211		NO ABNORMALITIES DETECTED
212		NO ABNORMALITIES DETECTED
213		NO ABNORMALITIES DETECTED
214		NO ABNORMALITIES DETECTED
215		NO ABNORMALITIES DETECTED
216		NO ABNORMALITIES DETECTED
217		NO ABNORMALITIES DETECTED
218		NO ABNORMALITIES DETECTED
219		NO ABNORMALITIES DETECTED
220		NO ABNORMALITIES DETECTED
221		NO ABNORMALITIES DETECTED
222		NO ABNORMALITIES DETECTED
223		NO ABNORMALITIES DETECTED
224		NO ABNORMALITIES DETECTED
225		NO ABNORMALITIES DETECTED

DRAFT

APPENDIX A

STUDY NO.: TRL 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 3.0 MG BASE/KG/DAY (WR242511)

ANIMAL#	ORGAN	OBSERVATION
251		NO ABNORMALITIES DETECTED
252		ANIMAL DIED PRIOR TO NECROPSY
253		NO ABNORMALITIES DETECTED
254		NO ABNORMALITIES DETECTED
255	LUNG	MULTIPLE WHITE FOCI, ALL LOBES
256		NO ABNORMALITIES DETECTED
257		ANIMAL DIED PRIOR TO NECROPSY
258		NO ABNORMALITIES DETECTED
259		NO ABNORMALITIES DETECTED
260		NO ABNORMALITIES DETECTED
261		ANIMAL DIED PRIOR TO NECROPSY
262	SEMINAL VESICLE	SMALL, LEFT
263		NO ABNORMALITIES DETECTED
264		ANIMAL DIED PRIOR TO NECROPSY
265		NO ABNORMALITIES DETECTED
266		NO ABNORMALITIES DETECTED
267		ANIMAL DIED PRIOR TO NECROPSY
268	LUNG	MULTIPLE/WHITE FOCI, ALL LOBES
269		NO ABNORMALITIES DETECTED
270		NO ABNORMALITIES DETECTED
271	LUNG	MOTTLED, WHITE, ALL LOBES
	EPIDIDYMIS	SMALL, RIGHT
	TESTES	SMALL, RIGHT
272	SEMINAL VESICLES	SMALL, BILATERAL
273		ANIMAL DIED PRIOR TO NECROPSY
274		NO ABNORMALITIES DETECTED
275		NO ABNORMALITIES DETECTED

DRAFT

DRAFT

APPENDIX B

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 1 0 MG BASE/KG/DAY VEHICLE

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
101	2.18	1.33	0.73	2.29	3.69
102	2.22	1.26	0.78	1.31	3.14
103	2.12	1.48	1.18	1.66	3.87
104	2.03	1.22	0.96	2.41	3.46
105	2.10	1.46	0.79	1.80	3.55
106	2.27	1.27	0.87	1.47	3.31
107	2.12	1.33	1.07	2.26	3.58
108	2.15	1.42	0.79	1.79	3.53
109	2.28	1.48	0.81	2.19	3.45
110	2.16	1.39	1.24	2.13	3.63
111	2.18	1.19	0.84	2.32	2.89
112	2.18	1.57	1.28	1.60	3.72
113	2.12	1.38	1.30	1.88	3.47
114	2.20	1.34	1.15	1.63	3.36
115	2.27	1.37	1.16	1.37	3.76
116	2.04	1.30	1.16	1.93	3.32
117	2.13	1.38	1.17	1.58	3.17
118	2.17	1.44	0.85	1.38	3.41
119	2.15	1.59	1.65	1.94	4.05
120	2.22	1.32	1.12	2.26	3.57
121	2.15	1.22	1.09	1.73	3.12
122	2.06	1.42	1.29	1.49	3.36
123	2.10	1.54	1.27	1.87	4.11
124	2.31	1.66	1.07	2.38	3.66
125	2.28	1.34	0.96	2.15	3.54

DRAFT

APPENDIX B

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 2 0.3 MG BASE/KG/DAY WR242511

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
151	2.06	1.40	1.23	1.80	3.64
152	2.05	1.39	0.81	2.11	3.51
153	2.22	1.41	1.20	2.01	3.70
154	1.97	1.34	1.12	1.24	3.14
155	2.09	1.33	0.94	1.82	3.38
156	2.17	1.45	1.18	1.37	3.77
157	2.20	1.39	0.94	1.38	3.54
158	2.32	1.50	1.14	1.77	3.60
159	2.24	1.36	1.10	1.67	3.58
160	2.00	1.28	1.02	2.23	3.48
161	2.22	1.22	1.40	1.99	3.43
162	2.14	1.31	0.99	2.02	3.52
163	2.10	1.42	0.97	1.31	3.75
164	2.15	1.45	1.04	2.50	3.28
165	2.04	1.36	0.87	2.37	3.37
166	2.15	1.56	1.08	2.53	3.81
167	2.10	1.21	0.65	2.15	3.54
168	2.20	1.41	1.59	2.59	3.63
169	2.25	1.49	1.31	1.67	3.63
170	2.06	1.29	1.06	2.05	3.42
171	2.16	1.36	1.00	2.98	3.44
172	2.24	1.27	1.14	1.63	3.32
173	2.20	1.51	1.07	2.21	3.24
174	2.13	1.35	1.01	2.26	3.74
175	2.24	1.65	1.13	2.31	3.92

DRAFT

APPENDIX B

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 3 1.0 MG BASE/KG/DAY WR242511

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
201	2.18	1.57	1.12	1.90	3.70
202	2.14	1.41	0.83	1.45	3.92
203	2.10	1.30	1.09	1.70	3.21
204	2.14	1.27	0.82	2.63	3.44
205	2.19	1.25	0.96	1.47	3.24
206	2.32	1.43	0.94	2.08	3.84
207	1.98	1.42	1.05	1.61	3.61
208	2.30	1.35	0.88	2.38	3.38
209	2.06	1.50	1.10	1.98	3.21
210	2.16	1.50	0.86	2.15	3.69
211	2.05	1.54	1.04	1.45	4.32
212	2.25	1.58	0.94	1.62	3.86
213	2.26	1.35	1.11	1.55	3.42
214	2.23	1.34	0.93	2.45	3.15
215	2.12	1.46	1.26	1.78	3.45
216	2.13	1.35	0.77	1.35	2.89
217	2.13	1.37	0.69	2.22	3.45
218	2.12	1.28	1.17	1.56	3.30
219	2.18	1.49	1.16	1.17	3.85
220	2.24	1.58	1.02	2.24	3.45
221	2.15	1.42	0.92	2.08	3.37
222	2.05	1.36	1.04	1.70	3.61
223	2.11	1.35	1.04	1.64	3.89
224	2.26	1.45	0.92	2.01	3.81
225	2.14	1.49	1.00	1.94	3.59

DRAFT

APPENDIX B

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 4 3.0 MG BASE/KG/DAY WR242511

Animal No.		BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
251		2.27	1.27	0.72	1.49	3.81
252	a					
253		1.95	1.37	0.78	1.45	3.93
254		2.11	1.37	0.91	1.65	3.40
255		2.41	1.50	0.83	2.11	3.69
256		2.17	1.30	0.88	1.34	3.53
257	a					
258		2.05	1.31	0.72	1.57	3.43
259		2.09	1.19	0.49	1.35	3.09
260		2.25	1.56	0.60	1.26	3.99
261	a					
262		2.20	1.28	0.92	1.69	3.71
263		2.27	1.16	0.80	1.23	3.64
264	a					
265		2.19	1.43	0.52	1.31	4.04
266		2.23	1.29	1.09	1.23	3.54
267	a					
268		2.18	1.31	0.91	1.80	3.38
269		2.28	1.19	1.15	1.24	3.21
270		2.15	1.20	0.65	1.62	3.29
271		2.12	1.01	0.84	1.92	2.22
272		2.03	1.20	0.54	0.94	3.34
273	a					
274		2.10	1.40	0.60	0.79	3.60
275		2.05	1.32	0.52	1.34	3.72

a Animals died prior to necropsy.

DRAFT

APPENDIX C

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 1 0 MG BASE/KG/DAY VEHICLE

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
101	2.18	0.61	0.33	1.05	1.69
102	2.22	0.57	0.35	0.59	1.41
103	2.12	0.70	0.56	0.78	1.83
104	2.03	0.60	0.47	1.19	1.70
105	2.10	0.69	0.38	0.86	1.69
106	2.27	0.56	0.38	0.65	1.46
107	2.12	0.63	0.50	1.07	1.69
108	2.15	0.66	0.37	0.83	1.64
109	2.28	0.65	0.36	0.96	1.51
110	2.16	0.64	0.57	0.99	1.68
111	2.18	0.55	0.39	1.06	1.33
112	2.18	0.72	0.59	0.73	1.71
113	2.12	0.65	0.61	0.89	1.64
114	2.20	0.61	0.52	0.74	1.53
115	2.27	0.60	0.51	0.60	1.66
116	2.04	0.64	0.57	0.95	1.63
117	2.13	0.65	0.55	0.74	1.49
118	2.17	0.66	0.39	0.64	1.57
119	2.15	0.74	0.77	0.90	1.88
120	2.22	0.59	0.50	1.02	1.61
121	2.15	0.57	0.51	0.80	1.45
122	2.06	0.69	0.63	0.72	1.63
123	2.10	0.73	0.60	0.89	1.96
124	2.31	0.72	0.46	1.03	1.58
125	2.28	0.59	0.42	0.94	1.55

DRAFT

APPENDIX C

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 2 0.3 MG BASE/KG/DAY WR242511

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
151	2.06	0.68	0.60	0.87	1.77
152	2.05	0.68	0.39	1.03	1.71
153	2.22	0.64	0.54	0.91	1.67
154	1.97	0.68	0.57	0.63	1.59
155	2.09	0.64	0.45	0.87	1.62
156	2.17	0.67	0.54	0.63	1.74
157	2.20	0.63	0.43	0.63	1.61
158	2.32	0.65	0.49	0.76	1.55
159	2.24	0.61	0.49	0.75	1.60
160	2.00	0.64	0.51	1.11	1.74
161	2.22	0.55	0.63	0.90	1.54
162	2.14	0.61	0.46	0.94	1.64
163	2.10	0.68	0.46	0.62	1.79
164	2.15	0.67	0.48	1.16	1.53
165	2.04	0.67	0.43	1.16	1.65
166	2.15	0.73	0.50	1.18	1.77
167	2.10	0.58	0.31	1.02	1.69
168	2.20	0.64	0.72	1.18	1.65
169	2.25	0.66	0.58	0.74	1.61
170	2.06	0.63	0.51	0.99	1.66
171	2.16	0.63	0.46	1.38	1.59
172	2.24	0.57	0.51	0.73	1.48
173	2.20	0.69	0.49	1.00	1.47
174	2.13	0.63	0.47	1.06	1.76
175	2.24	0.74	0.50	1.03	1.75

DRAFT

APPENDIX C

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 3 1.0 MG BASE/KG/DAY WR242511

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
201	2.18	0.72	0.51	0.87	1.70
202	2.14	0.66	0.39	0.68	1.83
203	2.10	0.62	0.52	0.81	1.53
204	2.14	0.59	0.38	1.23	1.61
205	2.19	0.57	0.44	0.67	1.48
206	2.32	0.62	0.40	0.90	1.66
207	1.98	0.72	0.53	0.81	1.82
208	2.30	0.59	0.38	1.03	1.47
209	2.06	0.73	0.53	0.96	1.56
210	2.16	0.69	0.40	1.00	1.71
211	2.05	0.75	0.51	0.71	2.11
212	2.25	0.70	0.42	0.72	1.72
213	2.26	0.60	0.49	0.69	1.51
214	2.23	0.60	0.42	1.10	1.41
215	2.12	0.69	0.59	0.84	1.63
216	2.13	0.63	0.36	0.63	1.36
217	2.13	0.64	0.32	1.04	1.62
218	2.12	0.60	0.55	0.74	1.56
219	2.18	0.68	0.53	0.54	1.77
220	2.24	0.71	0.46	1.00	1.54
221	2.15	0.66	0.43	0.97	1.57
222	2.05	0.66	0.51	0.83	1.76
223	2.11	0.64	0.49	0.78	1.84
224	2.26	0.64	0.41	0.89	1.69
225	2.14	0.70	0.47	0.91	1.68

DRAFT

APPENDIX C

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 4 3.0 MG BASE/KG/DAY WR242511

Animal No.		BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
251		2.27	0.56	0.32	0.66	1.68
252	a					
253		1.95	0.70	0.40	0.74	2.01
254		2.11	0.65	0.43	0.78	1.61
255		2.41	0.62	0.34	0.88	1.53
256		2.17	0.60	0.41	0.62	1.63
257	a					
258		2.05	0.64	0.35	0.77	1.67
259		2.09	0.57	0.23	0.65	1.48
260		2.25	0.69	0.27	0.56	1.77
261	a					
262		2.20	0.58	0.42	0.77	1.69
263		2.27	0.51	0.35	0.54	1.60
264	a					
265		2.19	0.65	0.24	0.60	1.84
266		2.23	0.58	0.49	0.55	1.59
267	a					
268		2.18	0.60	0.42	0.83	1.55
269		2.28	0.52	0.50	0.54	1.41
270		2.15	0.56	0.30	0.75	1.53
271		2.12	0.48	0.40	0.91	1.05
272		2.03	0.59	0.27	0.46	1.64
273	a					
274		2.10	0.67	0.29	0.38	1.71
275		2.05	0.64	0.25	0.65	1.81

a Animals died prior to necropsy.

DRAFT

APPENDIX D

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 1 0 MG BASE/KG/DAY VEHICLE

Animal No.	% Motility	Total Count (million/gram)
101	100	795.5
102	99	948.8
103	100	593.5
104	100	1255.0
105	96	1462.9
106	99	1166.7
107	100	908.3
108	90	857.1
109	99	2132.9
110	90	676.4
111	98	1290.6
112	99	1393.0
113	0	190.6
114	100	896.7
115	97	611.6
116	100	439.7
117	99	786.8
118	100	600.0
119	99	946.7
120	100	694.3
121	99	482.1
122	100	645.3
123	100	705.8
124	99	534.3
125	99	893.3

DRAFT

APPENDIX D

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 2 0.3 MG BASE/KG/DAY WR242511

Animal No.	% Motility	Total Count (million/gram)
151	100	979.4
152	100	540.0
153	99	1488.8
154	100	706.2
155	98	891.4
156	97	1144.7
157	99	1276.8
158	98	538.8
159	97	1157.1
160	93	827.5
161	99	888.6
162	98	801.1
163	99	625.7
164	93	1214.9
165	99	772.9
166	92	308.6
167	98	758.5
168	92	694.3
169	100	906.4
170	100	1232.5
171	100	479.8
172	100	658.6
173	100	578.5
174	98	975.3
175	99	1892.7

DRAFT

APPENDIX D

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 3 1.0 MG BASE/KG/DAY WR242511

Animal No.	% Motility	Total Count (million/gram)
201	99	1355.4
202	99	1187.1
203	99	799.4
204	99	1074.4
205	99	1005.8
206	98	565.2
207	97	480.6
208	99	462.8
209	100	1037.2
210	100	698.4
211	100	1682.2
212	99	332.2
213	99	993.5
214	100	1072.2
215	100	578.5
216	100	368.6
217	99	1041.4
218	99	689.8
219	96	1326.8
220	100	702.2
221	98	492.8
222	99	1008.3
223	99	878.5
224	97	1551.4
225	99	887.1

DRAFT

APPENDIX D

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR 242511 TARTRATE IN RATS

Study No.: TRL 197

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 4 3.0 MG BASE/KG/DAY WR242511

Animal No.	% Motility	Total Count (million/gram)
251	100	734.3
252	a	a
253	98	810.0
254	100	516.6
255	99	593.0
256	96	1272.8
257	a	a
258	98	981.4
259	b	870.0
260	100	412.7
261	a	a
262	99	1126.9
263	99	1009.8
264	a	a
265	100	714.4
266	97	249.9
267	a	a
268	99	609.7
269	98	664.1
270	99	2015.3
271	95	192.8
272	99	930.9
273	a	a
274	97	1328.7
275	97	842.4

a Animals died prior to necropsy.
b No files available for analysis.

APPENDIX E

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

STUDY NO.: TRL 197

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 1 (0 MG BASE/KG/DAY VEHICLE)

Animal No.	Normal	Head				Tail			
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
101	199	0	1	0	0	0	0	0	0
102	208	3	0	0	0	0	0	0	0
103	195	5	0	0	0	0	0	0	0
104	198	1	0	0	0	0	0	0	2
105	206	0	0	0	0	0	0	0	0
106	191	9	0	0	0	0	0	0	0
107	200	0	0	0	0	0	0	0	0
108	197	3	0	0	0	0	0	0	0
109	199	1	0	0	0	0	0	0	0
110	196	4	0	0	0	0	0	0	0
111	195	7	0	0	0	0	0	0	0
112	200	0	0	0	0	0	0	0	0
113	200	0	0	0	0	0	0	0	0
114	197	2	0	0	0	0	0	0	1
115	197	3	0	0	0	0	0	0	0
116	199	1	0	0	0	0	0	0	0
117	199	1	0	0	0	0	0	0	0
118	197	3	0	0	0	0	0	0	0
119	199	1	0	0	0	0	0	0	0
120	200	0	0	0	0	0	0	0	0
121	198	2	0	0	0	0	0	0	0
122	199	2	0	0	0	0	0	0	0
123	200	0	0	0	0	0	0	0	0
124	200	0	0	0	0	0	0	0	0
125	200	0	0	0	0	0	0	0	0

DRAFT

APPENDIX E

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR242511 TARTRATE IN RATS

STUDY NO.: TRL 197

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 2 (0.3 MG BASE/KG/DAY WR242511)

Animal		Head				Tail			
No.	Normal	Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
151	200	0	0	0	0	0	0	0	0
152	197	5	0	0	0	0	0	0	0
153	201	2	0	0	0	0	0	0	0
154	198	2	0	0	0	0	0	0	0
155	193	7	0	0	0	0	0	0	0
156	202	0	0	0	0	0	0	0	0
157	203	1	0	0	0	0	0	0	0
158	200	0	0	0	0	0	0	0	0
159	201	0	0	0	0	0	0	0	0
160	200	0	0	0	0	0	0	0	0
161	196	4	0	0	0	0	0	0	0
162	195	5	0	0	0	0	0	0	0
163	200	0	0	0	0	0	0	0	0
164	195	4	0	0	0	1	0	0	0
165	201	0	0	0	0	0	0	0	0
166	200	0	0	0	0	0	0	0	0
167	198	2	0	0	0	0	0	0	0
168	202	0	0	0	0	0	0	0	0
169	200	0	0	0	0	0	0	0	0
170	200	0	0	0	0	0	0	0	0
171	197	3	0	0	0	0	0	0	0
172	195	5	0	0	0	0	0	0	0
173	200	0	0	0	0	0	0	0	0
174	202	0	0	0	0	0	0	0	0
175	198	2	0	0	0	0	0	0	0

DRAFT

APPENDIX E

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR242511 TARTRATE IN RATS

STUDY NO.: TRL 197

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 3 (1.0 MG BASE/KG/DAY WR242511)

Animal No.	Normal	Head				Tail			
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
201	200	0	0	0	0	0	0	0	0
202	197	3	0	0	0	0	0	0	0
203	201	0	0	0	0	0	0	0	0
204	200	1	0	0	0	0	0	0	0
205	182	17	0	0	0	0	0	0	3
206	198	2	0	0	0	0	0	0	0
207	200	1	0	0	0	0	0	0	0
208	193	8	0	0	0	0	0	0	2
209	200	0	0	0	0	0	0	0	0
210	200	0	0	0	0	0	0	0	0
211	193	8	0	0	0	0	0	0	0
212	199	1	0	0	0	0	0	0	0
213	200	0	0	0	0	0	0	0	0
214	198	1	0	0	0	0	0	0	1
215	200	0	0	0	0	0	0	0	0
216	198	2	0	0	0	0	0	0	0
217	198	2	0	0	0	0	0	0	0
218	204	0	0	0	0	0	0	0	0
219	202	0	0	0	0	0	0	0	0
220	200	0	0	0	0	0	0	0	0
221	200	0	0	0	0	0	0	0	0
222	199	1	0	0	0	0	0	0	0
223	204	0	0	0	0	0	0	0	0
224	200	0	0	0	0	0	0	0	0
225	196	4	0	0	0	0	0	0	0

DRAFT

APPENDIX E

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR242511 TARTRATE IN RATS

STUDY NO.: TRL 197

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 4 (3.0 MG BASE/KG/DAY WR242511)

Animal No.		Head				Tail			
	Normal	Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
251	200	0	0	0	0	0	0	0	0
252 a									
253	201	2	0	0	0	0	0	0	0
254	203	1	0	0	0	0	0	0	0
255	197	3	0	0	0	0	0	0	0
256	199	2	0	0	0	0	0	0	0
257 a									
258	205	0	0	0	0	0	0	0	0
259	194	6	0	0	0	0	0	0	0
260	200	0	0	0	0	0	0	0	0
261 a									
262	205	0	0	0	0	0	0	0	0
263	200	1	0	0	0	0	0	0	0
264 a									
265	194	5	1	0	0	0	0	0	0
266	200	0	0	0	0	0	0	0	0
267 a									
268	199	1	0	0	0	0	0	0	0
269	204	0	0	0	0	0	0	0	0
270	198	2	0	0	0	0	0	0	0
271	199	1	0	0	0	0	0	0	0
272	197	3	0	0	0	0	0	0	0
273 a									
274	198	0	0	0	0	0	0	0	3
275	201	0	0	0	0	0	0	0	0

a Animals died prior to necropsy.

DRAFT

DRAFT

APPENDIX D

INDIVIDUAL FEMALE DATA: PRECOHABITATION AND COHABITATION PERIODS

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F GROUP: 1-F SEX: FEMALE
DAY 1-DAY 34 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
126	Normal			DAY 1-DAY 29
127	Normal			DAY 1-DAY 18
128	Normal Sacrificed			DAY 1-DAY 33 DAY 34
129	Normal			DAY 1-DAY 18
130	Normal			DAY 1-DAY 16
131	Normal			DAY 1-DAY 16
132	Normal			DAY 1-DAY 23
133	Normal			DAY 1-DAY 23
134	Normal			DAY 1-DAY 15
135	Normal			DAY 1-DAY 15
136	Normal			DAY 1-DAY 23
137	Normal			DAY 1-DAY 16
138	Normal			DAY 1-DAY 16
139	Normal			DAY 1-DAY 18
140	Normal			DAY 1-DAY 15
141	Normal			DAY 1-DAY 16
142	Normal			DAY 1-DAY 16
143	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F
DAY 1-DAY 34

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
144	Normal			DAY 1-DAY 15
145	Normal			DAY 1-DAY 17
146	Normal			DAY 1-DAY 15
147	Normal			DAY 1-DAY 15
148	Normal			DAY 1-DAY 15
149	Normal			DAY 1-DAY 18
150	Normal			DAY 1-DAY 18

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F GROUP: 2-F SEX: FEMALE
DAY 1-DAY 34 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
176	Normal			DAY 1-DAY 17
177	Normal			DAY 1-DAY 19
178	Normal			DAY 1-DAY 16
179	Normal			DAY 1-DAY 15
180	Normal			DAY 1-DAY 18
181	Normal			DAY 1-DAY 15
182	Normal			DAY 1-DAY 17
183	Normal Sacrificed			DAY 1-DAY 33 DAY 34
184	Normal			DAY 1-DAY 18
185	Normal			DAY 1-DAY 19
186	Normal			DAY 1-DAY 15
187	Normal			DAY 1-DAY 16
188	Normal			DAY 1-DAY 15
189	Normal			DAY 1-DAY 17
190	Normal			DAY 1-DAY 16
191	Normal			DAY 1-DAY 15
192	Normal			DAY 1-DAY 15
193	Normal			DAY 1-DAY 15

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F
DAY 1-DAY 34

GROUP: 2-F
DOSE: 0.3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
194	Normal			DAY 1-DAY 17
195	Normal			DAY 1-DAY 18
196	Normal			DAY 1-DAY 16
197	Normal			DAY 1-DAY 15
198	Normal			DAY 1-DAY 15
199	Normal			DAY 1-DAY 17
200	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F GROUP: 3-F SEX: FEMALE
DAY 1-DAY 34 DOSE: 1 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
226	Normal			DAY 1-DAY 16
227	Normal			DAY 1-DAY 15
228	Normal			DAY 1-DAY 16
229	Normal			DAY 1-DAY 15
230	Normal			DAY 1-DAY 15
231	Normal			DAY 1-DAY 17
232	Normal			DAY 1-DAY 16
233	Normal			DAY 1-DAY 15
234	Normal Sacrificed			DAY 1-DAY 33 DAY 34
235	Normal			DAY 1-DAY 16
236	Normal			DAY 1-DAY 15
237	Normal			DAY 1-DAY 15
238	Normal			DAY 1-DAY 15
239	Normal			DAY 1-DAY 16
240	Normal			DAY 1-DAY 28
241	Normal			DAY 1-DAY 18
242	Normal			DAY 1-DAY 15
243	Normal			DAY 1-DAY 18

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F
DAY 1-DAY 34

GROUP: 3-F
DOSE: 1 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
244	Normal			DAY 1-DAY 15
245	Normal			DAY 1-DAY 18
246	Normal			DAY 1-DAY 16
247	Normal			DAY 1-DAY 16
248	Normal			DAY 1-DAY 16
249	Normal			DAY 1-DAY 18
250	Normal			DAY 1-DAY 19

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F
DAY 1-DAY 34

GROUP: 4-F
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
276	Normal			DAY 1-DAY 15
277	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
278	Normal			DAY 1-DAY 15
279	Normal			DAY 1-DAY 16
280	Normal			DAY 1-DAY 15
281	Normal			DAY 1-DAY 15
282	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
283	Normal			DAY 1-DAY 15
284	Normal			DAY 1-DAY 16
285	Normal			DAY 1-DAY 33
	Sacrificed			DAY 34
286	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
287	Normal			DAY 1-DAY 15
288	Normal			DAY 1-DAY 16
289	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
290	Normal			DAY 1-DAY 18
291	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197F
DAY 1-DAY 34

GROUP: 4-F
DOSE: 3(mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
292	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
293	Normal			DAY 1-DAY 33
	Sacrificed			DAY 34
294	Normal			DAY 1-DAY 16
295	Normal			DAY 1-DAY 16
296	Normal			DAY 1-DAY 15
297	Normal			DAY 1-DAY 16
298	Normal			DAY 1-DAY 26
	Sacrificed			DAY 27
299	Normal			DAY 1-DAY 18
300	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F
DAY 1					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 2					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 3					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 4					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 5					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 6					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 7					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 8					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 9					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 10					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F
DAY 11					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 12					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 13					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 14					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 15					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 16					
No. Observed		17	15	16	16
Normal		17 100%	15 100%	16 100%	16 100%
DAY 17					
No. Observed		11	11	8	10
Normal		11 100%	11 100%	8 100%	10 100%
DAY 18					
No. Observed		10	6	7	10
Normal		10 100%	6 100%	7 100%	10 100%
DAY 19					
No. Observed		5	3	3	8
Normal		5 100%	3 100%	3 100%	8 100%
DAY 20					
No. Observed		5	1	2	8
Normal		5 100%	1 100%	2 100%	8 100%
DAY 21					

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F
	No. Observed	5	1	2	8
	Normal	5 100%	1 100%	2 100%	8 100%
DAY 22					
	No. Observed	5	1	2	8
	Normal	5 100%	1 100%	2 100%	8 100%
DAY 23					
	No. Observed	5	1	2	8
	Normal	5 100%	1 100%	2 100%	8 100%
DAY 24					
	No. Observed	2	1	2	8
	Normal	2 100%	1 100%	2 100%	8 100%
DAY 25					
	No. Observed	2	1	2	8
	Normal	2 100%	1 100%	2 100%	8 100%
DAY 26					
	No. Observed	2	1	2	8
	Normal	2 100%	1 100%	2 100%	8 100%
DAY 27					
	No. Observed	2	1	2	8
	Normal	2 100%	1 100%	2 100%	2 25%
	Sacrificed	0	0	0	6 75%
DAY 28					
	No. Observed	2	1	2	2
	Normal	2 100%	1 100%	2 100%	2 100%
DAY 29					
	No. Observed	2	1	1	2
	Normal	2 100%	1 100%	1 100%	2 100%
DAY 30					
	No. Observed	1	1	1	2
	Normal	1 100%	1 100%	1 100%	2 100%
DAY 31					

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1 3-F	3 4-F
	No. Observed	1	1	1	2
	Normal	1 100%	1 100%	1 100%	2 100%
DAY 32					
	No. Observed	1	1	1	2
	Normal	1 100%	1 100%	1 100%	2 100%
DAY 33					
	No. Observed	1	1	1	2
	Normal	1 100%	1 100%	1 100%	2 100%
DAY 34					
	No. Observed	1	1	1	2
	Sacrificed	1 100%	1 100%	1 100%	2 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197F GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29
126	239	249	256	265	274	274	298	305	322	306
127	231	242	247	253	253	257	--	--	--	--
128	239	245	256	260	266	271	--	--	--	--
129	209	211	205	227	223	217	--	--	--	--
130	229	237	236	250	258	261	--	--	--	--
131	227	231	238	241	246	244	--	--	--	--
132	216	227	228	236	239	245	260	271	--	--
133	235	246	251	259	265	265	281	294	--	--
134	250	259	267	265	271	281	--	--	--	--
135	220	225	233	234	244	252	--	--	--	--
136	238	257	272	272	266	271	--	--	--	--
137	233	239	243	248	256	262	--	--	--	--
138	232	234	241	239	249	261	--	--	--	--
139	215	227	228	230	231	234	--	--	--	--
140	220	228	236	235	238	250	--	--	--	--
141	235	241	244	261	255	265	--	--	--	--
142	242	245	255	262	265	279	--	--	--	--
143	237	247	251	247	247	257	--	--	--	--
144	226	233	235	235	239	249	--	--	--	--
145	223	230	235	243	255	257	--	--	--	--
146	246	268	274	279	283	287	--	--	--	--
147	230	240	252	260	262	269	--	--	--	--
148	218	224	230	226	230	238	--	--	--	--
149	217	226	232	234	233	237	--	--	--	--
150	230	242	243	246	247	244	--	--	--	--
MEAN	229	238	244	248	252	257	280	290	322	306
S.D.	10.4	12.7	15.3	14.7	15.2	16.4	19.0	17.3	--	--
N	25	25	25	25	25	25	3	3	1	1

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197F GROUP: 2-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29
176	234	243	246	248	258	265	--	--	--	--
177	224	230	234	247	246	245	252	--	--	--
178	216	221	227	236	240	243	--	--	--	--
179	236	245	250	252	253	269	--	--	--	--
180	244	253	260	265	266	269	--	--	--	--
181	228	242	250	252	258	264	--	--	--	--
182	233	237	246	251	258	262	--	--	--	--
183	230	241	241	251	252	262	--	--	--	--
184	238	248	257	261	264	260	--	--	--	--
185	219	234	238	237	248	249	253	--	--	--
186	218	223	231	226	234	242	--	--	--	--
187	240	242	251	262	260	269	--	--	--	--
188	245	251	261	264	265	279	--	--	--	--
189	231	241	247	256	260	267	--	--	--	--
190	208	210	216	225	228	239	--	--	--	--
191	230	237	243	241	250	255	--	--	--	--
192	238	247	252	255	257	266	--	--	--	--
193	248	256	264	269	275	279	--	--	--	--
194	238	244	251	261	270	272	--	--	--	--
195	224	233	240	247	253	257	--	--	--	--
196	223	224	228	237	237	244	--	--	--	--
197	234	241	251	252	259	270	--	--	--	--
198	216	224	227	230	232	240	--	--	--	--
199	217	227	235	242	248	251	--	--	--	--
200	229	233	238	230	234	240	--	--	--	--
MEAN	230	237	243	248	252	258	253	--	--	--
S.D.	10.3	11.2	12.0	12.6	12.5	12.7	0.7	--	--	--
N	25	25	25	25	25	25	2	0	0	0

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197F GROUP: 3-F SEX: FEMALE
DOSE: 1(mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29
226	235	238	246	257	263	271	--	--	--	--
227	244	245	251	252	258	265	--	--	--	--
228	230	230	237	244	236	250	--	--	--	--
229	227	231	248	238	247	256	--	--	--	--
230	232	237	241	239	236	250	--	--	--	--
231	209	217	222	230	229	233	--	--	--	--
232	216	214	217	227	229	240	--	--	--	--
233	238	246	252	252	257	262	--	--	--	--
234	240	234	240	248	251	261	--	--	--	--
235	219	224	231	233	239	249	--	--	--	--
236	229	238	248	248	252	262	--	--	--	--
237	217	225	230	230	231	228	--	--	--	--
238	230	232	241	238	247	259	--	--	--	--
239	223	230	230	239	238	245	--	--	--	--
240	222	233	239	241	256	256	277	291	305	--
241	233	238	244	253	259	261	--	--	--	--
242	227	232	241	245	244	257	--	--	--	--
243	234	238	243	254	256	260	--	--	--	--
244	239	250	258	264	271	275	--	--	--	--
245	216	226	232	227	231	234	--	--	--	--
246	247	244	251	260	264	272	--	--	--	--
247	245	259	260	263	269	276	--	--	--	--
248	217	221	235	237	229	247	--	--	--	--
249	233	240	249	256	266	265	--	--	--	--
250	238	247	253	267	273	274	283	--	--	--
MEAN	230	235	242	246	249	256	280	291	305	--
S.D.	10.2	10.5	10.7	11.9	14.4	13.3	4.2	--	--	--
N	25	25	25	25	25	25	2	1	1	0

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197F GROUP: 4-F SEX: FEMALE
DOSE: 3(mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29
276	234	241	242	247	240	251	--	--	--	--
277	235	243	246	247	255	250	--	--	--	--
278	230	238	235	231	231	238	--	--	--	--
279	224	235	232	237	234	242	--	--	--	--
280	229	236	236	237	237	245	--	--	--	--
281	223	229	231	228	231	240	--	--	--	--
282	236	243	251	260	265	280	--	--	--	--
283	231	240	242	244	247	256	--	--	--	--
284	251	250	257	266	268	273	--	--	--	--
285	246	255	255	254	260	264	--	--	--	--
286	224	225	228	228	221	235	--	--	--	--
287	217	225	225	223	221	234	--	--	--	--
288	239	247	253	253	251	262	--	--	--	--
289	219	228	229	233	234	242	--	--	--	--
290	227	239	241	238	240	241	--	--	--	--
291	230	233	236	241	240	247	--	--	--	--
292	238	242	248	249	252	262	--	--	--	--
293	237	244	246	246	251	256	--	--	--	--
294	216	223	225	225	225	239	--	--	--	--
295	242	250	250	253	246	253	--	--	--	--
296	239	239	238	240	243	251	--	--	--	--
297	232	244	247	248	253	259	--	--	--	--
298	215	216	210	217	216	217	--	--	--	--
299	212	224	230	235	236	238	--	--	--	--
300	219	219	215	208	206	225	--	--	--	--
MEAN	230	236	238	240	240	248	--	--	--	--
S.D.	10.2	10.3	12.1	13.6	15.3	14.3	--	--	--	--
N	25	25	25	25	25	25	0	0	0	0

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197F GROUP: 1-F SEX: FEMALE
DOSE: 0(mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	TOTAL GAIN
126	7	9	9	0	24	7	17	-16	57
127	5	6	0	4	--	--	--	--	15
128	11	4	6	5	--	--	--	--	26
129	-6	22	-4	-6	--	--	--	--	6
130	-1	14	8	3	--	--	--	--	24
131	7	3	5	-2	--	--	--	--	13
132	1	8	3	6	15	11	--	--	44
133	5	8	6	0	16	13	--	--	48
134	8	-2	6	10	--	--	--	--	22
135	8	1	10	8	--	--	--	--	27
136	15	0	-6	5	--	--	--	--	14
137	4	5	8	6	--	--	--	--	23
138	7	-2	10	12	--	--	--	--	27
139	1	2	1	3	--	--	--	--	7
140	8	-1	3	12	--	--	--	--	22
141	3	17	-6	10	--	--	--	--	24
142	10	7	3	14	--	--	--	--	34
143	4	-4	0	10	--	--	--	--	10
144	2	0	4	10	--	--	--	--	16
145	5	8	12	2	--	--	--	--	27
146	6	5	4	4	--	--	--	--	19
147	12	8	2	7	--	--	--	--	29
148	6	-4	4	8	--	--	--	--	14
149	6	2	-1	4	--	--	--	--	11
150	1	3	1	-3	--	--	--	--	2
MEAN	5	5	4	5	18	10	17	-16	22
S.D.	4.4	6.3	4.8	5.0	4.9	3.1	--	--	13.1
N	25	25	25	25	3	3	1	1	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197F GROUP: 2-F SEX: FEMALE
DOSE: 0.3(mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	TOTAL GAIN
176	3	2	10	7	--	--	--	--	22
177	4	13	-1	-1	7	--	--	--	22
178	6	9	4	3	--	--	--	--	22
179	5	2	1	16	--	--	--	--	24
180	7	5	1	3	--	--	--	--	16
181	8	2	6	6	--	--	--	--	22
182	9	5	7	4	--	--	--	--	25
183	0	10	1	10	--	--	--	--	21
184	9	4	3	-4	--	--	--	--	12
185	4	-1	11	1	4	--	--	--	19
186	8	-5	8	8	--	--	--	--	19
187	9	11	-2	9	--	--	--	--	27
188	10	3	1	14	--	--	--	--	28
189	6	9	4	7	--	--	--	--	26
190	6	9	3	11	--	--	--	--	29
191	6	-2	9	5	--	--	--	--	18
192	5	3	2	9	--	--	--	--	19
193	8	5	6	4	--	--	--	--	23
194	7	10	9	2	--	--	--	--	28
195	7	7	6	4	--	--	--	--	24
196	4	9	0	7	--	--	--	--	20
197	10	1	7	11	--	--	--	--	29
198	3	3	2	8	--	--	--	--	16
199	8	7	6	3	--	--	--	--	24
200	5	-8	4	6	--	--	--	--	7
MEAN	6	5	4	6	6	--	--	--	22
S.D.	2.5	5.1	3.6	4.5	2.1	--	--	--	5.3
N	25	25	25	25	2	0	0	0	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197F GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	TOTAL GAIN
226	8	11	6	8	--	--	--	--	33
227	6	1	6	7	--	--	--	--	20
228	7	7	-8	14	--	--	--	--	20
229	17	-10	9	9	--	--	--	--	25
230	4	-2	-3	14	--	--	--	--	13
231	5	8	-1	4	--	--	--	--	16
232	3	10	2	11	--	--	--	--	26
233	6	0	5	5	--	--	--	--	16
234	6	8	3	10	--	--	--	--	27
235	7	2	6	10	--	--	--	--	25
236	10	0	4	10	--	--	--	--	24
237	5	0	1	-3	--	--	--	--	3
238	9	-3	9	12	--	--	--	--	27
239	0	9	-1	7	--	--	--	--	15
240	6	2	15	0	21	14	14	--	72
241	6	9	6	2	--	--	--	--	23
242	9	4	-1	13	--	--	--	--	25
243	5	11	2	4	--	--	--	--	22
244	8	6	7	4	--	--	--	--	25
245	6	-5	4	3	--	--	--	--	8
246	7	9	4	8	--	--	--	--	28
247	1	3	6	7	--	--	--	--	17
248	14	2	-8	18	--	--	--	--	26
249	9	7	10	-1	--	--	--	--	25
250	6	14	6	1	9	--	--	--	36
MEAN	7	4	4	7	15	14	14	--	24
S.D.	3.5	5.8	5.3	5.2	8.5	--	--	--	12.4
N	25	25	25	25	2	1	1	0	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197F GROUP: 4-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	TOTAL GAIN
276	1	5	-7	11	--	--	--	--	10
277	3	1	8	-5	--	--	--	--	7
278	-3	-4	0	7	--	--	--	--	0
279	-3	5	-3	8	--	--	--	--	7
280	0	1	0	8	--	--	--	--	9
281	2	-3	3	9	--	--	--	--	11
282	8	9	5	15	--	--	--	--	37
283	2	2	3	9	--	--	--	--	16
284	7	9	2	5	--	--	--	--	23
285	0	-1	6	4	--	--	--	--	9
286	3	0	-7	14	--	--	--	--	10
287	0	-2	-2	13	--	--	--	--	9
288	6	0	-2	11	--	--	--	--	15
289	1	4	1	8	--	--	--	--	14
290	2	-3	2	1	--	--	--	--	2
291	3	5	-1	7	--	--	--	--	14
292	6	1	3	10	--	--	--	--	20
293	2	0	5	5	--	--	--	--	12
294	2	0	0	14	--	--	--	--	16
295	0	3	-7	7	--	--	--	--	3
296	-1	2	3	8	--	--	--	--	12
297	3	1	5	6	--	--	--	--	15
298	-6	7	-1	1	--	--	--	--	1
299	6	5	1	2	--	--	--	--	14
300	-4	-7	-2	19	--	--	--	--	6
MEAN	2	2	1	8	--	--	--	--	12
S.D.	3.5	3.9	4.0	5.1	--	--	--	--	7.7
N	25	25	25	25	0	0	0	0	25

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION[a] (Grams)

STUDY: 197F GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
126	30.0	18.3	28.8	20.7	33.0	19.7
127	18.3	15.7	20.8	19.7	17.5	20.0
128	18.0	16.3	19.0	19.0	18.5	16.7
129	20.8	13.0	18.5	17.7	20.3	14.0
130	17.8	15.7	17.3	18.3	21.5	16.7
131	17.0	15.3	17.0	16.0	15.8	13.7
132	17.5	15.7	18.5	17.0	20.0	16.0
133	21.5	17.7	19.5	18.3	20.0	16.7
134	24.3	16.3	22.0	16.7	20.0	19.7
135	33.8	19.3	20.0	16.7	22.0	19.0
136	18.5	20.0	22.5	20.7	17.3	15.0
137	27.5	17.7	24.8	23.3	29.3	23.3
138	19.8	14.7	18.3	16.7	21.5	18.0
139	18.8	16.7	16.0	15.0	22.8	15.3
140	18.0	15.7	18.0	16.3	18.8	18.3
141	19.8	16.0	20.5	19.7	19.5	16.7
142	21.8	17.3	20.5	20.3	27.8	20.0
143	18.0	17.0	19.8	20.3	21.0	20.3
144	20.0	16.7	17.3	16.0	18.0	18.0
145	17.8	15.7	16.8	16.7	20.8	16.0
146	27.3	20.3	20.0	18.0	27.0	18.0
147	18.5	17.7	19.0	18.0	18.3	19.3
148	16.8	15.3	17.3	16.0	17.5	17.7
149	18.3	16.3	17.5	16.0	17.8	15.7
150	22.3	19.0	27.3	18.3	29.3	19.7
MEAN	20.9	16.8	19.9	18.1	21.4	17.7
S.D.	4.42	1.70	3.17	2.00	4.44	2.26
N	25	25	25	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197F GROUP: 2-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
176	20.0	17.3	21.3	19.7	23.0	19.0
177	21.0	17.0	22.0	20.0	19.5	16.3
178	16.5	17.7	19.8	18.7	22.8	17.3
179	17.8	18.3	20.0	17.3	20.8	20.7
180	21.5	17.3	20.0	17.0	19.5	18.7
181	18.3	17.7	19.0	17.7	29.5	17.7
182	18.3	16.3	20.3	17.3	21.5	16.7
183	18.3	15.7	17.5	17.7	18.3	17.0
184	19.8	17.7	20.5	17.7	22.5	16.7
185	14.8	16.7	17.3	15.3	19.8	15.3
186	17.3	16.0	18.3	16.3	23.3	17.7
187	18.0	16.3	19.3	18.7	18.8	17.3
188	22.0	17.7	19.8	19.0	18.8	19.7
189	17.8	16.0	18.0	17.0	18.3	15.7
190	17.0	13.7	16.3	17.3	18.8	15.3
191	23.5	14.7	17.8	17.0	19.0	17.3
192	17.0	15.7	17.3	16.3	20.5	16.0
193	19.8	18.7	21.5	19.0	20.8	19.7
194	17.3	15.7	17.3	17.0	18.5	16.7
195	20.0	18.3	23.0	19.0	24.0	16.7
196	16.0	14.3	17.0	17.0	23.5	15.7
197	20.0	18.7	18.8	18.3	20.5	17.7
198	23.8	15.7	15.8	17.3	17.5	16.3
199	16.8	17.0	17.5	17.0	18.8	16.0
200	20.0	15.7	17.8	14.7	16.8	15.0
MEAN	18.9	16.6	18.9	17.6	20.6	17.1
S.D.	2.28	1.34	1.86	1.27	2.73	1.49
N	25	25	25	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197F GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
226	18.3	16.3	18.8	18.7	20.0	17.3
227	20.0	14.3	18.3	16.3	23.0	16.3
228	14.5	16.0	18.0	16.7	18.3	16.7
229	17.3	16.0	--	16.3	19.0	16.7
230	21.5	15.7	22.0	17.3	16.8	18.3
231	22.3	14.3	19.5	15.7	25.8	15.0
232	17.5	13.7	15.8	16.3	21.0	15.7
233	18.8	17.0	19.3	18.3	20.3	17.0
234	18.8	17.3	21.5	18.7	22.0	19.7
235	16.3	16.0	--	16.7	25.8	15.7
236	20.0	22.7	20.0	16.7	19.5	18.3
237	15.3	14.7	14.8	13.0	15.3	12.3
238	16.5	15.3	17.5	15.3	25.3	17.7
239	17.3	16.3	15.5	16.0	19.0	14.7
240	18.0	17.3	17.8	13.7	21.3	17.3
241	16.8	16.0	17.8	17.3	18.3	17.0
242	17.5	15.7	17.8	17.0	17.8	18.3
243	22.3	17.3	19.3	20.0	18.5	18.3
244	21.5	17.0	18.0	17.7	25.5	18.3
245	16.8	16.7	16.3	15.0	18.5	16.7
246	34.5	19.0	25.5	18.7	33.5	18.7
247	20.0	19.3	19.0	17.0	25.3	16.7
248	26.8	21.0	42.5	18.7	38.5	20.3
249	20.8	16.7	20.5	17.0	22.3	16.3
250	18.3	17.0	19.3	19.3	20.0	18.7
MEAN	19.5	16.7	19.8	16.9	22.0	17.1
S.D.	4.11	2.03	5.46	1.66	5.19	1.69
N	25	25	23	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197F GROUP: 4-F SEX: FEMALE
DOSE: 3(mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
276	19.5	18.7	18.0	17.3	16.8	16.7
277	26.8	17.7	17.3	15.7	18.3	14.7
278	22.3	16.7	17.0	11.0	15.8	14.0
279	19.8	17.0	15.8	14.3	14.3	14.7
280	18.5	17.3	17.8	15.0	21.3	15.7
281	16.5	16.3	15.8	13.3	14.8	15.7
282	21.3	17.0	19.5	16.0	24.5	19.7
283	20.5	16.3	15.3	14.7	17.5	16.3
284	19.0	16.3	19.8	17.0	29.5	14.3
285	19.3	18.0	17.8	14.0	23.0	14.7
286	18.3	17.3	16.8	14.0	25.8	13.3
287	23.8	16.0	19.5	17.3	38.5	19.0
288	18.8	17.7	16.5	13.7	14.8	15.3
289	21.8	19.0	17.5	16.3	28.5	15.0
290	20.3	17.3	16.5	12.0	15.8	13.7
291	20.8	17.7	17.3	14.3	17.3	14.3
292	18.0	17.0	17.5	15.7	16.8	16.0
293	17.5	17.0	17.3	14.7	17.5	17.0
294	16.8	16.0	17.8	0.5	--	14.7
295	20.8	18.3	19.5	17.0	21.8	13.7
296	20.0	17.0	14.0	13.7	16.3	15.7
297	22.8	15.7	17.3	16.0	19.0	17.3
298	18.3	15.7	15.3	13.7	17.3	12.3
299	19.3	17.0	18.8	15.7	17.5	16.0
300	18.5	15.0	16.3	11.7	21.0	15.7
MEAN	20.0	17.0	17.3	14.2	20.2	15.4
S.D.	2.30	0.96	1.45	3.32	5.77	1.68
N	25	25	25	25	24	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day -7

DRAFT

APPENDIX E

INDIVIDUAL FEMALE DATA: GESTATION PERIOD

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 0(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
126	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
127	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
129	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
130	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
131	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
134	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
135	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
137	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
138	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
139	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
140	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
141	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
142	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
143	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
144	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
145	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
146	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
147	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
148	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
149	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
150	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 0.3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
176	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
177	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
178	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
179	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
180	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
181	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
182	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
184	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
185	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
186	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
187	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
188	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
189	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 0.3(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
190	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
191	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
192	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
193	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
194	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
195	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
196	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
197	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
198	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
199	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
200	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 1.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
226	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
227	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
228	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
229	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
230	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
231	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
232	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
233	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
235	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
236	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
237	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
238	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
239	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 1.0(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
240	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
241	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
242	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
243	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
244	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
245	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
246	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
247	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
248	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
249	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
250	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 3.0(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
276	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
278	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
279	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
280	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
281	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
283	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
284	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
287	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
288	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
290	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
291	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
294	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
295	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 197 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 16 DOSE: 3.0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
296	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
297	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
299	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16
300	Normal			DAY 0-DAY 15
	Scheduled Sacrifice			DAY 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197 SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1.0 3-F	3.0 4-F
DAY 0					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 1					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 2					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 3					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 4					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 5					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 6					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 7					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 8					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 9					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR242511 TARTRATE
IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 197 SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	0.3 2-F	1.0 3-F	3.0 4-F
DAY 10					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 11					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 12					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 13					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 14					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 15					
No. Observed		21	24	24	17
Normal		21 100%	24 100%	24 100%	17 100%
DAY 16					
No. Observed		21	24	24	17
Scheduled Sacrifice		21 100%	24 100%	24 100%	17 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16
126	310	317	324	331	330	337	338	363	373	405
127	263	272	283	286	286	290	295	317	328	352
129	238	247	258	267	269	277	279	304	315	337
130	262	272	275	281	280	286	283	299	310	331
131	244	258	267	264	269	277	277	302	309	345
132	--	--	--	--	--	--	--	--	--	--
133	--	--	--	--	--	--	--	--	--	--
134	279	295	301	303	298	308	315	331	350	376
135	251	259	260	267	266	271	275	290	308	332
136	--	--	--	--	--	--	--	--	--	--
137	268	274	282	283	291	297	295	321	334	361
138	260	274	285	283	285	292	295	317	325	351
139	240	250	250	255	255	260	265	285	291	316
140	247	258	264	265	266	270	277	292	308	333
141	268	285	291	291	299	306	311	343	360	389
142	283	296	299	303	308	313	316	345	361	388
143	264	274	282	287	294	298	299	322	343	367
144	258	262	270	275	272	279	286	305	319	349
145	265	278	275	280	286	285	286	311	321	348
146	282	296	306	308	307	317	321	342	361	382
147	267	275	284	283	285	288	290	309	322	335
148	239	248	256	258	258	263	263	279	298	325
149	246	250	256	260	259	262	270	284	297	317
150	258	262	271	277	277	279	285	300	321	350
MEAN	262	272	278	281	283	288	291	312	326	352
S.D.	17.5	18.5	18.8	18.7	19.0	19.9	19.6	22.5	23.5	24.8
N	21	21	21	21	21	21	21	21	21	21

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197 GROUP: 2-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16
176	264	277	284	292	298	299	303	330	343	361
177	255	267	268	272	278	282	287	306	325	341
178	244	251	259	262	265	268	269	288	298	330
179	270	280	285	288	286	291	299	317	330	353
180	279	287	290	294	295	299	306	326	344	373
181	264	277	284	287	284	293	296	318	319	348
182	259	265	275	283	284	290	293	316	323	347
184	276	287	299	306	314	311	325	346	355	386
185	258	268	271	273	276	279	283	294	314	344
186	244	252	259	261	264	264	271	289	305	339
187	273	281	286	292	295	298	305	323	334	369
188	282	295	305	308	310	320	316	345	361	387
189	270	281	279	289	292	292	297	314	321	343
190	236	248	253	259	265	273	275	290	314	335
191	257	269	277	281	284	287	288	314	331	352
192	267	280	290	290	291	297	300	319	339	366
193	288	296	300	302	313	314	314	338	362	388
194	275	285	289	278	294	292	297	317	329	351
195	269	274	275	282	283	289	292	304	321	340
196	253	258	264	267	268	271	274	293	309	336
197	265	284	286	289	290	296	297	319	336	354
198	244	255	260	256	260	267	267	286	303	317
199	257	263	275	275	276	281	284	303	312	324
200	241	260	266	270	277	279	281	313	341	364
MEAN	262	273	278	282	285	289	292	313	328	352
S.D.	13.8	13.9	14.0	14.6	15.1	14.7	15.3	17.3	17.6	19.2
N	24	24	24	24	24	24	24	24	24	24

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16
226	268	287	292	287	298	302	303	330	353	383
227	266	279	280	286	292	295	294	316	333	357
228	249	255	263	265	272	279	277	302	305	336
229	260	271	277	281	287	289	293	317	342	368
230	249	263	268	273	277	282	290	313	329	340
231	238	248	252	255	259	262	263	287	304	328
232	241	250	254	260	259	269	265	292	306	333
233	266	279	284	285	286	292	296	320	339	354
235	255	268	273	271	277	281	278	307	320	342
236	263	274	279	281	281	285	290	310	335	363
237	227	237	247	254	253	262	263	280	286	280
238	259	270	280	284	289	293	299	330	348	381
239	245	262	260	263	262	268	269	292	297	326
240	304	308	308	318	323	325	336	356	378	401
241	278	281	285	294	295	299	304	320	331	353
242	254	268	266	272	275	281	284	305	327	347
243	272	280	286	291	292	295	311	324	338	360
244	277	290	294	299	298	303	310	331	345	380
245	259	266	272	278	283	278	286	313	335	355
246	274	286	288	287	296	300	299	326	344	372
247	279	290	296	292	296	303	304	331	339	379
248	248	262	271	270	278	283	281	310	330	362
249	275	285	292	294	295	293	307	321	330	355
250	293	294	303	305	307	316	318	332	352	377
MEAN	262	273	278	281	285	289	293	315	331	356
S.D.	17.7	16.4	16.0	15.8	16.4	15.7	18.2	17.0	20.3	25.0
N	24	24	24	24	24	24	24	24	24	24

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 197 GROUP: 4-F SEX: FEMALE
DOSE: 3.0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16
276	245	265	270	270	267	276	285	302	322	353
278	235	248	253	258	263	266	271	294	316	336
279	242	264	262	264	267	271	270	296	313	337
280	240	258	258	262	266	270	272	296	320	344
281	239	255	253	258	258	261	268	291	315	342
283	256	266	275	273	274	279	285	301	319	342
284	273	293	293	298	301	305	308	342	350	387
287	237	250	254	261	259	268	273	294	311	340
288	255	266	270	268	278	280	282	315	331	368
290	244	253	258	263	265	266	274	295	309	339
291	249	259	263	266	265	269	275	295	308	333
294	211	236	241	241	249	252	256	289	310	320
295	259	273	275	271	276	285	281	317	330	356
296	251	268	273	271	276	279	284	312	329	382
297	266	278	282	278	281	288	283	313	320	344
299	245	256	260	266	265	269	279	298	315	337
300	223	233	234	244	239	248	249	270	280	300
MEAN	245	260	263	265	268	272	276	301	318	345
S.D.	14.9	14.6	14.6	12.7	13.6	13.5	12.9	15.5	14.3	20.8
N	17	17	17	17	17	17	17	17	17	17

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg base/kg/day)

ANIMAL #	DAY 1[c]	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16	TOTAL GAIN
126	7	7	7	-1	7	1	25	10	32	95
127	9	11	3	0	4	5	22	11	24	89
129	9	11	9	2	8	2	25	11	22	99
130	10	3	6	-1	6	-3	16	11	21	69
131	14	9	-3	5	8	0	25	7	36	101
132	--	--	--	--	--	--	--	--	--	--
133	--	--	--	--	--	--	--	--	--	--
134	16	6	2	-5	10	7	16	19	26	97
135	8	1	7	-1	5	4	15	18	24	81
136	--	--	--	--	--	--	--	--	--	--
137	6	8	1	8	6	-2	26	13	27	93
138	14	11	-2	2	7	3	22	8	26	91
139	10	0	5	0	5	5	20	6	25	76
140	11	6	1	1	4	7	15	16	25	86
141	17	6	0	8	7	5	32	17	29	121
142	13	3	4	5	5	3	29	16	27	105
143	10	8	5	7	4	1	23	21	24	103
144	4	8	5	-3	7	7	19	14	30	91
145	13	-3	5	6	-1	1	25	10	27	83
146	14	10	2	-1	10	4	21	19	21	100
147	8	9	-1	2	3	2	19	13	13	68
148	9	8	2	0	5	0	16	19	27	86
149	4	6	4	-1	3	8	14	13	20	71
150	4	9	6	0	2	6	15	21	29	92
MEAN	10	7	3	2	5	3	21	14	25	90
S.D.	3.8	3.8	3.2	3.6	2.6	3.1	5.1	4.6	4.8	13.0
N	21	21	21	21	21	21	21	21	21	21

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

[c]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197 GROUP: 2-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 1[c]	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16	TOTAL GAIN
176	13	7	8	6	1	4	27	13	18	97
177	12	1	4	6	4	5	19	19	16	86
178	7	8	3	3	3	1	19	10	32	86
179	10	5	3	-2	5	8	18	13	23	83
180	8	3	4	1	4	7	20	18	29	94
181	13	7	3	-3	9	3	22	1	29	84
182	6	10	8	1	6	3	23	7	24	88
184	11	12	7	8	-3	14	21	9	31	110
185	10	3	2	3	3	4	11	20	30	86
186	8	7	2	3	0	7	18	16	34	95
187	8	5	6	3	3	7	18	11	35	96
188	13	10	3	2	10	-4	29	16	26	105
189	11	-2	10	3	0	5	17	7	22	73
190	12	5	6	6	8	2	15	24	21	99
191	12	8	4	3	3	1	26	17	21	95
192	13	10	0	1	6	3	19	20	27	99
193	8	4	2	11	1	0	24	24	26	100
194	10	4	-11	16	-2	5	20	12	22	76
195	5	1	7	1	6	3	12	17	19	71
196	5	6	3	1	3	3	19	16	27	83
197	19	2	3	1	6	1	22	17	18	89
198	11	5	-4	4	7	0	19	17	14	73
199	6	12	0	1	5	3	19	9	12	67
200	19	6	4	7	2	2	32	28	23	123
MEAN	10	6	3	4	4	4	20	15	24	90
S.D.	3.7	3.6	4.3	4.1	3.3	3.5	4.8	6.2	6.2	13.2
N	24	24	24	24	24	24	24	24	24	24

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

[c]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197 GROUP: 3-F SEX: FEMALE
DOSE: 1.0(mg base/kg/day)

ANIMAL #	DAY 1[c]	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16	TOTAL GAIN
226	19	5	-5	11	4	1	27	23	30	115
227	13	1	6	6	3	-1	22	17	24	91
228	6	8	2	7	7	-2	25	3	31	87
229	11	6	4	6	2	4	24	25	26	108
230	14	5	5	4	5	8	23	16	11	91
231	10	4	3	4	3	1	24	17	24	90
232	9	4	6	-1	10	-4	27	14	27	92
233	13	5	1	1	6	4	24	19	15	88
235	13	5	-2	6	4	-3	29	13	22	87
236	11	5	2	D	4	5	20	25	28	100
237	10	10	7	-1	9	1	17	6	-6	53
238	11	10	4	5	4	6	31	18	33	122
239	17	-2	3	-1	6	1	23	5	29	81
240	4	0	10	5	2	11	20	22	23	97
241	3	4	9	1	4	5	16	11	22	75
242	14	-2	6	3	6	3	21	22	20	93
243	8	6	5	1	3	16	13	14	22	88
244	13	4	5	-1	5	7	21	14	35	103
245	7	6	6	5	-5	8	27	22	20	96
246	12	2	-1	9	4	-1	27	18	28	98
247	11	6	-4	4	7	1	27	8	40	100
248	14	9	-1	8	5	-2	29	20	32	114
249	10	7	2	1	-2	14	14	9	25	80
250	1	9	2	2	9	2	14	20	25	84
MEAN	11	5	3	4	4	4	23	16	24	93
S.D.	4.2	3.3	3.8	3.4	3.3	5.2	5.1	6.3	9.0	14.3
N	24	24	24	24	24	24	24	24	24	24

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

[c]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 197 GROUP: 4-F SEX: FEMALE
DOSE: 3.0 (mg base/kg/day)

ANIMAL #	DAY 1[c]	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 10	DAY 13	DAY 16	TOTAL GAIN
276	20	5	0	-3	9	9	17	20	31	108
278	13	5	5	5	3	5	23	22	20	101
279	22	-2	2	3	4	-1	26	17	24	95
280	18	0	4	4	4	2	24	24	24	104
281	16	-2	5	0	3	7	23	24	27	103
283	10	9	-2	1	5	6	16	18	23	86
284	20	0	5	3	4	3	34	8	37	114
287	13	4	7	-2	9	5	21	17	29	103
288	11	4	-2	10	2	2	33	16	37	113
290	9	5	5	2	1	8	21	14	30	95
291	10	4	3	-1	4	6	20	13	25	84
294	25	5	0	8	3	4	33	21	10	109
295	14	2	-4	5	9	-4	36	13	26	97
296	17	5	-2	5	3	5	28	17	53	131
297	12	4	-4	3	7	-5	30	7	24	78
299	11	4	6	-1	4	10	19	17	22	92
300	10	1	10	-5	9	1	21	10	20	77
MEAN	15	3	2	2	5	4	25	16	27	99
S.D.	4.8	2.9	4.1	3.9	2.7	4.2	6.3	5.1	9.2	13.9
N	17	17	17	17	17	17	17	17	17	17

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period

[c]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 3[b]	DAY 6	DAY 10	DAY 13	DAY 16
126	21.3	25.0	27.0	23.7	25.7
127	28.0	20.7	23.8	21.7	23.0
129	24.0	23.7	25.8	24.3	23.3
130	22.0	20.0	20.8	22.7	22.7
131	20.3	20.7	23.0	22.3	25.3
132	--	--	--	--	--
133	--	--	--	--	--
134	22.7	22.3	26.3	24.3	27.7
135	21.7	19.3	20.8	22.0	23.7
136	--	--	--	--	--
137	23.0	26.3	27.5	27.0	29.7
138	24.3	20.0	22.3	24.3	26.3
139	28.3	17.7	18.8	20.7	23.7
140	20.0	21.3	22.0	23.0	24.0
141	32.3	25.0	28.0	27.3	27.0
142	28.7	24.3	29.3	29.3	28.0
143	25.3	24.0	26.5	26.3	27.0
144	22.3	22.3	24.5	25.3	27.3
145	22.7	19.7	22.0	23.0	25.3
146	23.0	23.0	25.0	25.0	27.0
147	19.3	20.0	21.3	24.0	23.0
148	21.0	20.0	19.5	22.0	25.0
149	32.3	18.7	21.5	20.7	22.3
150	29.0	23.0	33.8	28.0	38.3
MEAN	24.4	21.8	24.3	24.1	26.0
S.D.	3.90	2.36	3.67	2.38	3.49
N	21	21	21	21	21

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION[a] (Grams)

STUDY: 197 GROUP: 2-F SEX: FEMALE
DOSE: 0.3 (mg base/kg/day)

ANIMAL #	DAY 3[b]	DAY 6	DAY 10	DAY 13	DAY 16
176	26.3	26.0	27.0	29.0	27.0
177	22.3	21.3	24.0	23.0	24.3
178	21.3	20.3	22.5	24.0	25.3
179	23.3	24.7	24.3	26.0	29.0
180	22.0	21.0	25.3	--	26.3
181	21.3	20.7	23.0	20.3	23.3
182	21.0	21.0	21.8	24.3	26.0
184	35.7	26.0	27.5	26.3	26.3
185	20.7	18.3	20.3	21.0	23.7
186	20.3	21.3	22.5	23.3	24.0
187	21.3	20.7	22.3	23.3	27.0
188	22.3	23.0	26.3	25.3	28.0
189	22.3	20.7	21.5	22.3	23.3
190	22.3	20.3	21.8	24.3	24.0
191	25.7	20.3	29.3	25.7	23.0
192	46.3	20.0	24.8	24.0	27.3
193	22.7	25.3	27.3	29.7	30.3
194	22.3	20.0	20.8	22.0	23.0
195	35.7	21.0	19.5	21.3	26.7
196	21.7	19.0	36.3	25.7	26.3
197	21.0	21.0	21.5	24.7	25.7
198	19.0	20.0	22.3	22.3	22.3
199	22.0	22.3	22.5	23.0	23.3
200	22.3	23.0	25.8	27.7	29.0
MEAN	24.2	21.6	24.2	24.3	25.6
S.D.	6.26	2.09	3.62	2.43	2.20
N	24	24	24	23	24

--: Data Unavailable

[a] Calculated daily food consumption for successive period intervals

[b] Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197 GROUP: 3-F SEX: FEMALE
DOSE:[b] 1.0 (mg base/kg/day)

ANIMAL #	DAY 3	DAY 6	DAY 10	DAY 13	DAY 16
226	23.0	22.0	25.5	28.0	28.0
227	18.7	19.0	18.3	23.7	24.3
228	21.3	21.0	22.8	23.3	25.7
229	21.7	22.3	25.3	27.7	27.7
230	22.0	20.0	25.8	23.7	25.0
231	36.7	23.0	22.8	22.7	23.7
232	19.3	18.7	22.5	24.0	24.7
233	22.0	22.0	24.8	26.3	23.0
235	18.7	22.7	22.0	30.3	20.3
236	20.7	21.0	25.3	25.0	26.7
237	19.3	21.0	22.5	20.3	19.7
238	20.7	22.3	25.5	25.0	27.3
239	19.3	18.7	21.5	21.3	24.3
240	23.3	23.3	27.8	28.0	27.7
241	28.0	22.3	23.5	25.3	27.3
242	20.0	20.3	22.0	25.7	24.3
243	34.7	23.3	26.3	26.0	26.3
244	21.7	21.7	24.5	23.7	25.3
245	25.7	22.7	25.3	26.0	26.3
246	22.3	23.3	27.3	27.0	27.0
247	23.3	21.3	23.5	25.7	30.0
248	34.0	22.3	28.0	28.0	30.3
249	26.0	21.0	29.5	23.3	24.3
250	23.0	23.3	25.3	25.0	29.7
MEAN	23.6	21.6	24.5	25.2	25.8
S.D.	5.05	1.44	2.48	2.31	2.66
N	24	24	24	24	24

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 197 GROUP: 4-F SEX: FEMALE
DOSE: 3.0 (mg base/kg/day)

ANIMAL #	DAY 3[b]	DAY 6	DAY 10	DAY 13	DAY 16
276	21.7	22.7	24.3	27.7	27.7
278	18.3	20.3	22.8	27.0	29.3
279	20.3	19.7	24.0	26.7	27.0
280	19.3	19.7	25.5	24.7	25.3
281	17.7	18.7	21.5	27.0	26.3
283	19.7	19.3	21.3	23.7	23.0
284	24.7	21.3	26.8	27.3	29.7
287	28.0	24.0	26.3	27.0	28.7
288	17.7	18.7	23.0	25.0	26.0
290	22.7	19.3	21.3	22.0	24.3
291	18.0	18.3	20.5	24.0	25.0
294	25.3	17.7	22.3	24.7	22.3
295	21.0	21.3	25.8	29.3	29.7
296	18.3	20.3	24.0	25.3	25.7
297	22.3	20.0	25.3	26.0	28.3
299	24.7	21.3	23.3	25.7	26.0
300	23.0	19.0	24.0	22.3	22.7
MEAN	21.3	20.1	23.6	25.6	26.3
S.D.	3.09	1.62	1.89	1.94	2.39
N	17	17	17	17	17

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

[b]Baseline is day 0

DRAFT

APPENDIX F

INDIVIDUAL FEMALE REPRODUCTIVE DATA

- Individual Cesarean Section Data
- Individual Estrous Data

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
0.0	126	22	24	1	0	21	0	Normal
	127	17	18	2	0	15	2	Normal
	128	15	15	a	a	a	a	a
	129	17	28	0	0	17	0	Normal
	130	16	18	1	0	15	0	Normal
	131	17	17	1	0	16	0	Normal
	134	18	20	0	0	18	0	Normal
	135	18	18	1	0	17	0	Normal
	136	7	34	a	a	a	a	a
	137	16	20	1	0	14	1	Normal
	138	17	17	3	0	14	0	Normal
	139	14	16	1	0	13	0	Normal
	140	15	17	1	0	14	0	Normal
	141	19	19	1	0	18	0	Normal
	142	17	19	1	0	16	0	Normal
	143	18	19	0	0	18	0	Normal
	144	17	18	0	0	17	0	Normal
	145	17	26	0	0	17	0	Normal
	146	20	20	0	0	20	0	Normal
	147	12	14	0	0	12	0	Normal
	148	16	16	0	0	16	0	Normal
	149	16	16	0	0	16	0	Normal
	150	17	18	0	0	17	0	Normal

a = Animals Pregnant, GD0 Unknown

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
0.0	126	8	5	13
	127	6	12	17
	128	0	a	a
	129	39	0	39
	130	11	6	17
	131	0	6	6
	132	10	0	10
	135	0	6	6
	136	79	a	a
	137	20	13	30
	138	0	18	18
	139	13	7	19
	140	12	7	18
	141	0	5	5
	142	11	6	16
	143	5	0	5
	144	6	0	6
	145	35	0	35
	146	0	0	0
	147	14	0	14
	148	0	0	0
	149	0	0	0
	150	6	0	6

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
0.3	176	15	15	2	1	12	0	Normal
	177	14	17	0	0	14	0	Normal
	178	18	20	1	0	17	0	Normal
	179	15	15	1	0	14	0	Normal
	180	18	21	1	0	17	0	Normal
	181	16	17	0	0	16	0	Normal
	182	19	19	2	0	17	0	Normal
	183	17	23	a	a	a	a	a
	184	18	18	0	0	18	0	Normal
	185	15	15	1	0	14	0	Normal
	186	17	18	0	0	17	0	Normal
	187	18	18	1	0	17	0	Normal
	188	19	20	0	0	18	1	Normal
	189	14	20	0	0	14	0	Normal
	190	16	20	1	0	15	0	Normal
	191	15	19	0	0	15	0	Normal
	192	14	14	0	0	14	0	Normal
	193	18	19	1	0	17	0	Normal
	194	16	16	0	0	16	0	Normal
	195	17	19	1	0	16	0	Normal
	196	16	25	0	0	16	0	Normal
	197	13	18	1	0	13	0	Normal
	198	16	16	0	0	16	0	Normal
	199	15	16	4	0	11	0	Normal
	200	14	15	0	0	12	2	Normal

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
0.3	176	0	20	20
	177	18	0	18
	187	10	6	15
	179	D	7	7
	180	14	6	19
	187	6	0	6
	188	0	11	11
	187	26	a	a
	187	D	0	0
	185	D	7	7
	186	6	0	6
	187	0	6	6
	188	5	5	10
	187	30	0	30
	190	20	6	25
	195	21	0	21
	192	0	0	0
	193	5	6	11
	195	0	0	0
	195	11	6	16
	188	36	0	36
	195	28	0	28
	195	0	0	0
	199	6	27	31
	200	7	14	20

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTLITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
1.0	226	19	22	0	0	19	0	Normal
	227	18	18	1	0	17	0	Normal
	228	16	21	0	0	16	0	Normal
	229	17	17	0	0	17	0	Normal
	230	13	16	0	0	13	0	Normal
	231	16	21	1	0	15	0	Normal
	232	14	16	0	0	14	0	Normal
	233	18	19	2	0	16	0	Normal
	234	20	23	a	a	a	a	a
	235	15	21	0	0	15	0	Normal
	236	18	18	0	0	18	0	Normal
	237	5	20	5	0	0	0	Normal
	238	18	18	1	0	17	0	Normal
	239	13	14	0	1	12	0	Normal
	240	18	19	0	1	17	0	Normal
	241	15	20	1	0	14	0	Normal
	242	18	18	0	0	18	0	Normal
	243	19	21	0	0	19	0	Normal
	244	16	17	1	0	14	0	Normal
	245	18	22	0	0	18	0	Normal
	246	20	21	3	0	17	0	Normal
	247	19	20	2	0	17	0	Normal
	248	16	16	1	0	15	0	Normal
	249	16	25	0	0	16	0	Normal
	250	16	24	1	0	15	0	Normal

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
1.0	226	14	0	14
	227	0	6	6
	228	24	0	24
	227	0	0	0
	230	19	0	19
	242	24	6	29
	232	13	0	13
	233	5	11	16
	234	5	a	a
	235	29	0	29
	246	0	0	0
	237	75	100	100
	238	0	6	6
	249	7	8	14
	240	5	6	11
	242	25	7	30
	242	0	0	0
	242	10	0	10
	244	6	13	18
	245	18	0	18
	246	5	15	19
	249	5	11	15
	248	0	6	6
	249	36	0	36
	250	33	6	38

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
3.0	276	17	19	1	0	16	0	Normal
	278	16	17	1	0	15	0	Normal
	279	16	17	1	0	15	0	Normal
	280	15	16	0	0	15	0	Normal
	281	16	17	0	0	16	0	Normal
	283	16	23	1	0	15	0	Normal
	284	20	22	1	0	19	0	Normal
	285	11	14	a	a	a	a	a
	287	16	16	0	0	16	0	Normal
	288	20	21	1	0	19	0	Normal
	290	16	23	0	0	16	0	Normal
	291	13	13	0	0	13	0	Normal
	293	18	21	a	a	a	a	a
	294	13	14	1	0	12	0	Normal
	295	14	16	1	0	13	0	Normal
	296	15	15	1	0	14	0	Normal
	297	15	17	1	1	13	0	Normal
	299	14	16	2	0	12	0	Normal
	300	15	17	1	0	14	0	Normal

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
3.0	276	11	6	16
	279	6	6	12
	279	6	6	12
	280	6	0	6
	281	6	0	6
	283	30	6	35
	284	9	5	14
	285	9	a	a
	287	0	0	0
	288	5	5	10
	290	30	0	30
	291	0	0	0
	293	14	a	a
	293	7	8	14
	295	13	7	19
	296	0	7	7
	279	12	13	24
	299	13	14	25
	300	12	7	18

a = Animals Pregnant, GD0 Unknown

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
0	126	4	12	4.00	101	15
	127	4	12	4.00	102	4
	128	3	9	4.50	103	15
	129	4	10	3.33	104	4
	130	3	8	4.00	105	2
	136	4	9	4.00	106	2
	147	4	10	4.00	107	c
	133	4	11	3.67	107	c
	134	4	11	3.67	109	4
	135	4	11	3.67	110	4
	136	4	10	4.00	114	4
	137	4	12	4.00	112	2
	134	4	9	4.50	114	2
	149	4	12	4.00	114	4
	136	5	13	3.25	114	4
	147	4	12	4.00	116	2
	142	4	12	4.00	117	2
	136	4	11	3.67	114	1
	136	4	11	3.67	119	1
	145	4	11	3.67	122	4
	146	4	12	4.00	122	4
	147	4	11	3.67	122	4
	136	4	11	3.67	123	1
	149	4	12	4.00	124	4
	150	4	12	4.00	125	4

a = Animals Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Pregnant; Day 0 Unknown
c = Animal Non-Gravid
d = Animal Not Cohabited

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
0.3	176	3	9	4.50	151	3
	177	3	10	5.00	152	5
	178	4	12	4.00	154	2
	179	5	14	3.50	154	1
	180	4	12	4.00	155	4
	181	3	8	5.00	154	1
	182	4	13	4.33	154	3
	183	3	8	4.00	163	15
	184	4	11	3.67	159	4
	185	3	12	6.00	160	5
	186	4	11	3.67	163	1
	187	4	12	4.00	162	2
	188	4	11	3.67	163	1
	189	4	12	4.00	164	3
	190	4	13	4.33	163	2
	191	3	8	4.00	166	1
	192	5	14	3.50	167	1
	193	4	11	3.67	163	1
	194	a	a	a	169	3
	195	3	10	5.00	170	4
	196	4	13	4.33	174	2
	197	4	11	3.67	172	1
	198	4	11	3.67	173	1
	199	4	12	4.00	174	3
	200	4	10	3.33	175	1

a = Animals Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Pregnant; Day 0 Unknown
c = Animal Non-Gravid
d = Animal Not Cohabited

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
1.0	226	4	12	4.00	201	2
	227	4	11	3.67	202	1
	228	4	14	4.67	203	2
	229	4	8	4.00	204	1
	230	3	8	4.00	205	1
	236	4	11	5.00	206	3
	236	4	11	4.00	207	2
	244	4	11	3.67	208	1
	234	3	14	5.50	209	b
	235	4	8	4.00	210	2
	236	4	8	5.00	211	1
	237	4	11	3.67	212	1
	236	a	a	a	213	1
	244	4	11	4.33	214	2
	240	4	11	5.50	215	14
	241	4	11	4.67	216	4
	242	3	8	4.00	217	1
	244	4	10	5.00	218	4
	244	4	8	4.00	219	1
	246	4	12	5.00	220	4
	246	4	12	4.00	221	2
	244	4	10	5.00	222	2
	248	4	11	5.50	223	2
	249	4	11	3.67	224	4
	250	3	10	3.33	225	5

a = Animals Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Pregnant; Day 0 Unknown
c = Animal Non-Gravid
d = Animal Not Cohabited

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
3.0	276	4	11	3.67	251	1
	291	4	12	4.00	265	d
	288	4	12	3.67	253	1
	279	4	12	4.00	258	d
	280	4	11	3.67	255	1
	283	3	8	3.50	265	1
	282	4	12	4.00	267	d
	283	3	9	4.50	258	1
	283	4	12	4.00	259	1
	285	4	10	3.33	260	d
	288	4	12	4.00	265	d
	287	3	7	3.50	262	1
	288	a	8	a	265	1
	282	4	12	3.67	264	d
	290	4	12	4.00	265	d
	291	3	8	4.00	267	1
	292	4	12	4.00	267	d
	291	4	12	3.67	267	d
	294	3	9	4.50	269	2
	295	4	12	4.00	270	1
	298	4	12	3.67	271	1
	291	3	8	4.00	271	1
	298	3	8	4.00	271	d
	299	4	12	4.00	274	4
	300	a	a	a	275	1

a = Animals Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Pregnant; Day 0 Unknown
c = Animal Non-Gravid
d = Animal Not Cohabited

DRAFT

DRAFT

APPENDIX G

Protocol and Amendments

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR242511 TARTRATE IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine and evaluate the toxic potential of the test article on the reproductive capability of male and female rats. The scope of the study will encompass gonadal function, estrous cycles, mating, conception, implantation and early embryonic development. The experimental design of the study will involve administration of the test article to both sexes. In males, evaluation will include reproductive organ weights and sperm assessment (counts and motility). The protocol conforms with the FDA *Guideline on Detection of Toxicity to Reproduction for Medicinal Products* (1994), which was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Materiel Development Activity
2.2	Address:	Fort Detrick Frederick, MD 21702-5009.
2.3	Representative:	George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology 1940 W. Taylor St. Chicago, IL 60612-7353
3.3	Study Director:	Debra L. Kirchner, Ph.D., D.A.B.T.

4.0 DATES:

4.1 Proposed Initiation of Dosing Phase (Males):	10/20/95
4.2 Proposed Completion of In-Life Phase:	01/12/96
4.3 Proposed Study Completion Date (Draft Final Report):	04/12/96

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 11-6-95

5.0 TEST ARTICLE

5.1 Name or Code No: WR242511 Tartrate
8-[(4-Amino-1-methylbutyl)amino]5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL tartrate
Bottle Number - BM19356
Base Mole Fraction = 0.71

5.2 TRL Chemical No: 1720614

5.3 Physical Description: Yellow powder

5.4 Storage Conditions to Maintain Stability:

5.4.1 Temperature: -20 to -15°C.

5.4.2 Humidity: Ambient conditions at -20 to -15°C.

5.4.3 Light: Protect from light.

5.4.4 Special Requirements: None.

5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.

5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, unused test article may be returned to the Sponsor.

6.0 PERSONNEL:

Principal Investigator	Barry S. Levine, D.Sc., D.A.B.T.
Study Director	Debra L. Kirchner, Ph.D., D.A.B.T.
Sperm Assessment (PAI)	Michael D. Mercieca, B.S.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 11-1-95

7.0 TEST SYSTEM:

7.1	Species:	Rat
7.2	Strain:	CD® (Virus Antibody Free)
7.3	Sex(s)/Number:	100 virgin females received approximately 14 days after the males 100 virgin males
7.4	Age of Animals:	60 - 70 days old at randomization (assigned to study)
7.5	Body Weight:	Approximately 275 - 350 g (males) and 200 - 250 g (females) at randomization (assigned to study)
7.6	Source of Animals:	Charles River Breeding Laboratories, Inc. The specific source will be documented in the raw data.

7.7 Justification for Selection of Test System: The CD® rat was selected as the animal model for this study because; (1) the U.S. Food and Drug Administration *Guideline on Detection of Toxicity to Reproduction for Medicinal Products* (1994) requires a rodent species, preferably rats, for preclinical reproductive testing of drugs; (2) this species/strain has a proven sensitivity to a variety of agents and therefore provides a suitable animal model for testing chemicals and drugs for human risk assessment; (3) reliable scientific methods currently exist for performing rat reproduction studies; (4) historical data and experience exist; (5) the CD® rat has been used extensively for reproduction testing; and (6) it was specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Each animal will be given a study-unique number as a subcutaneously implanted microchip. This number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number, sex and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed (except during mating) in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, is adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for approximately 14 days. During the quarantine period, the animals will be observed daily for signs of illness, and all unusual observations will be documented and reported to the Study Director or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 11-2-95

Clinical Veterinarian prior to being placed on test. Unless deemed unhealthy (based on general clinical observations), all animals will be available for use in the study. If a selected animal appears unhealthy prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

7.11 Food: Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) will be provided *ad libitum* from arrival until termination.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is not treated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Group	No. of Animals Male	Female	Treatment	Dose Level (mg base/kg/day)	Dose Conc. (mg base/ml)	Dose Volume (ml/kg/day)
1	25	25	Vehicle	0	0	5
2	25	25	WR242511	0.3	0.06	5
3	25	25	WR242511	1.0	0.2	5
4	25	25	WR242511	3.0	0.6	5

One hundred ten males and one hundred twenty females will be purchased for the study. The additional females are necessary because a small percentage of females will typically not exhibit healthy vaginal cytology i.e., they will not cycle properly.

Test article dose levels are selected on the basis of a developmental toxicity study in female rats (UIC/TRL Study No. 144) and a three month toxicity study in male and female rats (UIC/TRL Study No. 107). The duration of the male premating dosing period is based on a lack of testicular toxicity in this latter study. The number of animals,

REVISED PAGE
STUDY NO: 197 INITIAL: dlc
DATE: 11-6-95

25/sex/dose level, is necessary to result in 16 - 20 litters/group for rodents as recommended in the *ICH Harmonized Tripartite Guideline* (1993).

8.2 Frequency and Route of Administration of Test Article: The test article will be given orally by gavage as follows:

Males: Daily for 29 days prior to cohabitation, during cohabitation, and following separation of males and females until the day prior to sacrifice (Section 8.8.7).

Females: Daily for 15 days prior to cohabitation, during cohabitation, and continuing through gestation day 6. Sperm negative animals will be dosed until the day prior to sacrifice (Section 8.8.6).

The drug will be given at a dosing volume of 5 ml/kg/day. The control group will receive the vehicle (i.e., the control article) at the same dosing volume. The specific volume to be administered will be adjusted on the basis of the animal's most recent body weight. All animals will receive the control article by gavage for three days during week -1 to acclimate them to the dosing procedure.

8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During week -1, animals judged to be healthy (based on general clinical observations) and meeting acceptable body weight requirements (Section 7.5) will be assigned to the study at random, within sex, using a randomization procedure on the basis of body weight. At the discretion of the Study Director, females that demonstrate acceptable reproductive health (as evidenced by vaginal cytology) but are outside of the acceptable body weight range may be utilized in the study. Similarly, at the discretion of the Study Director, females within the acceptable body weight range but not demonstrating acceptable reproductive health (as evidenced by vaginal cytology) may not be utilized on the study.

8.5 Control Article (Test Article Vehicle): 1% Methylcellulose/0.2% Tween 80. Both chemicals will be obtained from Sigma Chemical Co. If another source is used, it will be identified in the raw data.

8.6 Test Article Dosage Form Preparation and Analyses: The neat drug will be identified by GC-MS, and will be analyzed for purity prior to and after completion of the dosing period. Test article suspensions will be prepared on the basis of the mole fraction of the base, adjusted for purity. The 1% methylcellulose/0.2% Tween 80 vehicle will be prepared at least weekly by placing the required amount of deionized distilled water in a beaker and then adding the required amount of methylcellulose and volume of Tween 80, using its specific gravity of 1.08 (1.0 g of methylcellulose and 0.2 g Tween 80 per 100 ml of deionized distilled water). One lot no. each of methylcellulose and Tween 80 will be used. The mixture will be stirred until homogeneous and then refrigerated. The dosage formulations for the test article will be prepared daily by diluting a stock

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 3/3/92

formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The test article stock suspension will be prepared by adding the appropriate amount of WR242511 Tartrate (adjusted for purity) with the required volume of 1.0% methylcellulose/0.2% Tween 80 vehicle in a pre-calibrated beaker. The contents will be mixed with an Omni-Mixer homogenizer, for at least 5 minutes. All suspensions will be stored at 2 - 8°C. All suspensions will be allowed to warm to room temperature and stirred continuously before and during gavage administration. Samples of all dosing suspensions (including controls and stock suspensions) prepared on the first day of each week will be analyzed prior to use, and only suspensions within 10% of their target concentration will be used. As the actual dosing suspensions will be prepared daily from the stock, the suspensions will not be analyzed after use.

8.7 Breeding: Each female will be cohabitated with a single male from the same treatment group. Within litter cohabitation will not occur because males and females of the same age will arrive approximately 14 days apart. Cohabitation will commence after 29 days of dosing in males and after 15 days of dosing in females. Each mating pair will be observed for positive signs of copulation once daily during cohabitation. Detection of a vaginal copulatory plug or a positive vaginal smear (sperm present) will be considered as evidence of mating. The day on which positive evidence of mating is detected will be designated as gestation day 0 and will result in separation of the mating pair. The female will be returned to her individual cage.

At the end of the 3 week cohabitation period, sperm-negative females will be separated from their mates and placed in their own cage.

8.8 Type and Frequency of Observations, Test Analyses and Measurements:

8.8.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.

8.8.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing, and in the morning after completion of the dosing period for females. Moribund animals will be sacrificed on that day and necropsies will be performed as described in Section 8.8.8.

8.8.3 Body Weights:

Males: At randomization in week -1 and twice weekly (≈ every 3 - 4 days) during dosing. A final body weight will be recorded on the day of scheduled necropsy.

REVISED PAGE
STUDY NO: 197 INITIAL: JLK
DATE: 3/8/96

Females: At randomization in week -1 and twice weekly (≈ every 3 - 4 days) during dosing throughout the cohabitation phase. When positive evidence of mating is detected, body weights will be obtained during dosing on gestation days 0 through 6, and in the postdosing period on gestation days 10, 13, and 16.

8.8.4 Food Consumption:

Males: During week -1 and twice weekly (≈ every 3 - 4 days), except during cohabitation.

Females: During week -1 and twice weekly (≈ every 3 - 4 days), except during cohabitation. When positive evidence of mating is detected, food consumption will be measured during the following intervals: gestation days 0-3; 3-6; 6-10; 10-13; and 13-16.

8.8.5 Vaginal Cytology: Vaginal washings will be performed in all females to monitor the estrous cycle. Washings will be performed in the quarantine period for approximately 10 days prior to randomization. Washings will be performed daily during the dosing period throughout cohabitation until either evidence of copulation is observed or until termination of the cohabitation period.

8.8.6 Scheduled Necropsy of Females: Females with evidence of mating (i.e., sperm-positive females) will be euthanized by CO_2 asphyxiation and necropsied on presumed gestation day 16. Sperm-negative females not palpated pregnant will be sacrificed 16 days following the last day of cohabitation. At the discretion of the Study Director, sperm-negative females palpated pregnant may be sacrificed sooner than 16 days after the last day of cohabitation. These occurrences will be documented in the raw data.

At necropsy, the thoracic, abdominal and pelvic cavities will be opened and the viscera examined. Any abnormalities will be recorded. The uterus and ovaries will be removed from the body and examined. For sperm-positive females, uteri with macroscopic implantations will be opened and the number of implantation sites, viable and non-viable fetuses*, and resorptions will be recorded consecutively from the distal end of the left uterine horn to the cervix and then from the distal end of the right uterine horn to the cervix. The *corpora lutea* on each ovary will be counted and the number recorded. For sperm-negative, pregnant females, the number of implantation sites and *corpora lutea* will be recorded and used in the calculation of preimplantation loss and mating and fertility indices. Because the end of the dosing period, i.e., gestation day 6, is unknown, the number of viable and non-viable fetuses and resorption sites in these animals will be recorded and retained with the raw data, but will not be utilized in the statistical analysis.

REVISED PAGE
STUDY NO: 197 INITIAL: [illegible]
DATE: 12-5-95

*A viable fetus is defined as one that has pink, well vascularized tissue; a dark red placenta; and clean, reddish amniotic fluid. A non-viable fetus is defined as one that has white, non-vascularized tissue; a necrotic, green placenta; and cloudy, dark amniotic fluid.

Uteri with no macroscopic evidence of implantations will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

The necropsy procedure will include retention of the uterus and ovaries from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparison. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

8.8.7 Scheduled Necropsy of Males: Mating and fertility indices (Section 8.9) will be reviewed by the Study Director and Sponsor's Representative as soon as possible. If apparent adverse effects are noted, the Study Director and Sponsor's Representative will decide if any additional evaluations of the males are required. If no apparent test article related changes are observed, the males will be euthanized by CO_2 asphyxiation and necropsied. The thoracic, abdominal and pelvic cavities will be opened and the viscera examined. Any abnormalities will be recorded. Paired organ weights will be collected from each animal for the testes, epididymides and seminal vesicles. Prostate weights will also be recorded. If observable size, color or consistency differences are noted, the paired organs of the affected animal will be weighed separately. The brain will be weighed for organ to brain weight comparisons.

The necropsy procedure will include retention of both testes in Bouin's fixative, and the left epididymis, prostate, and both seminal vesicles from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparisons. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

At necropsy, sperm motility will be assessed. Semen samples will be evaluated utilizing the Hamilton Thorne Integrated Visual Optics System (IVOS) 10 Sperm analyzer. The motility sample will be prepared from the vas deferens and will be placed in a suspension medium containing PBS with 1% BSA (Bovine Serum Albumin). After a 3 minute "swim out" period, a 100 µ deep cannula will be inserted into the media and a sample will be drawn up. The cannula will be

REVISED PAGE
STUDY NO: 197 INITIAL: tlk
DATE: 11-6-95

inserted into the stage and the general examination of the sperm sample will be made on the computer monitor. Based on the results of the motility sample analyses, other parameters including straight-line, curvilinear and path velocities, progressive motility and cross-beat frequency may also be calculated. Sperm samples will be discarded after analysis.

At necropsy, the right epididymis will be trimmed, frozen on dry ice, and temporarily stored at -70°C or less for subsequent sperm counts and sperm morphology assessment. The epididymal samples will be thawed, and the caudal section will be weighed and minced, and one or two drops will be spread on a slide and stained with Eosin for sperm morphology assessment. The minced caudal epididymal samples will then be homogenized, and a 100 uL sample will be added to a vial containing a florescent dye which stains the DNA in the sperm head. A sample will be loaded into the IVOS and the stained sperm heads will be counted. The results will be reported as total sperm count adjusted for caudal epididymis weight (10^6 sperm/g tissue). Sperm samples will be discarded after analysis.

8.8.8 Unscheduled Deaths: All animals found dead or euthanized *in extremis* during the study and females that deliver early will be euthanized by CO_2 asphyxiation and grossly examined externally and internally. Body cavities (thoracic, abdominal, and pelvic) will be opened and examined. Uterine contents will be examined and the number of implants will be recorded. The number of *corpora lutea* on each ovary will be noted. Any abnormalities will be recorded. Organs/tissues with gross lesions will be saved in 10% neutral buffered formalin for possible histopathological examination. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

Uteri with no macroscopic evidence of implants will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

8.9 Statistical Analyses:

Body weights, body weight gains, calculated daily food consumption, and male organ to brain weight ratios will be analyzed by one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

Sperm counts, sperm morphology and sperm motility; the numbers of *corpora lutea*(C.L.), implantations, resorptions, viable and nonviable fetuses; and the percent preimplantation loss*, postimplantation loss**, and total implantation loss*** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 4/22/96

*Preimplantation loss% = [(# C.L. - # implantations)/#C.L.] x 100
**Postimplantation loss% = [(# implantations - # viable fetuses)/# implantations] x 100
***Total implantation loss % = [(#C.L. - # viable fetuses)/#C.L.] x 100

The following reproductive indices will be analyzed by Fisher's exact probability test.

Mating Index = (No. with evidence of mating/No. cohoused) x 100
Fertility Index = (No. pregnant/No. with evidence of mating) x 100

Sperm-negative pregnant females will be included in the analysis of the numbers of *corpora lutea* and implantations, the percent preimplantation loss, and the mating and fertility indices.

In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any changes in automated data entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the UIC/TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

REVISED PAGE
STUDY NO: 197 INITIAL: dlk
DATE: 4/22/96

Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? U.S. Food and Drug Administration
Does the Sponsor Request that test article samples be returned? Possibly; direction will be provided by the Sponsor.
Does the Sponsor request that samples of the test article/carrier mixture(s) be sent to the Sponsor? No

11.0 REFERENCES:

FDA (1994). International Conference on Harmonisation; Guideline on Detection of Toxicity to Reproduction for Medicinal Products. Federal Register, Thursday, 9/22/94.

Gad, S and Weil, CS (1988). Statistics and Experimental Design for Toxicologists, 2nd ed. pp 53-70, 147-176, Telforel Press. Caldwell, NJ.

Hayes, W (1989). Principles and Methods of Toxicology, pp 311-361, Raven press. New York, NY.

ICH (1993). ICH Harmonised Tripartite Guideline: Detection of Toxicity of Reproduction for Medicinal Products. International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

U.S. Department of Health and Human Services (1985). Guide for the Care and Use of Laboratory Animals. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publications No. 86-23.

12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Barry S. Levine for — Debra L. Kirchner, Ph.D., D.A.B.T. — 7/3/95 Date

PRINCIPAL INVESTIGATOR: Barry S. Levine — Barry S. Levine, D.Sc., D.A.B.T. — 7/3/95 Date

QUALITY ASSURANCE: Ronald Schoenbeck — Ronald Schoenbeck — 7/5/95 Date

SPONSOR APPROVAL: George J. Schieferstein — George J. Schieferstein, Ph.D. Contracting Officer's Representative (COR) — 7/10/95 Date

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-16
Study No.: 197

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

June 30, 1995

Appendix 1

Barry S. Levine
Med Pharmacology
312 BGRC, M/C 868:

Dear Dr. Levine:

The modifications requested in your correspondence of June 27, 1995, pertaining to your approved protocol ACC: 93-077.17: Oral Fertility and Early Embryonic Developmental Study of WR242511 Tartrate in Rats' have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago.

You will be pleased to know that the modifications were approved on June 30, 1995 and consequently the records of the Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

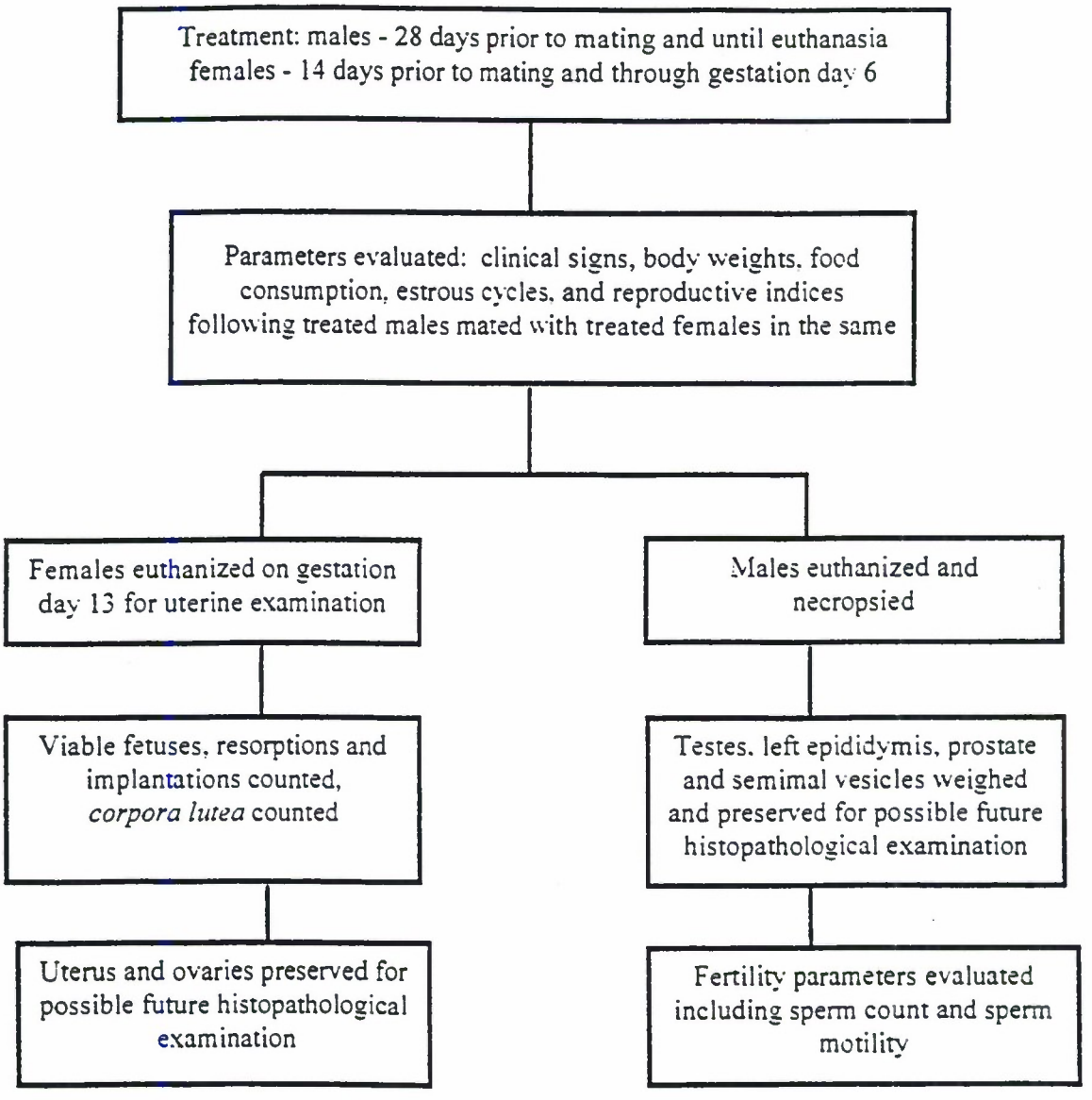
Sincerely yours,

Michael W. Levine, PhD
Chair, Animal Care Committee

MWL:st
xc:BRL

APPENDIX 2

Experimental Design



PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

1. Page 1 Section 2.1

Change "Material" to "Materiel".

Reason: To correct a spelling error.

2. Page 1 Section 4.0

Add the following change and dates:

Proposed Initiation of Dosing Phase (Males):	10/20/95
Proposed Completion of In-Life Phase:	01/12/96
Proposed Study Completion Date:	
(Draft Final Report:	04/12/96

Reason: A. To change "In-Life Phase" to "Dosing Phase (Males)"

B. Dates were not finalized when the protocol was submitted.

3. Page 2 Section 5.1

Change Bottle Number from "BM05816" to "BM19356".

Reason: To correctly identify the Bottle Number for WR242511 Tartrate in this study.

4. Page 3 Section 7.3

Add the following after "100 Virgin females" to read "100 Virgin females received approximately 14 days after the males"

Reason: To clarify that males and females will arrive in separate shipments.

5. Page 4/5 Section 8.1

Change "16 - 20 litters" in the last line of the 1st paragraph on page 5 to "16 - 20 litters/group".

Reason: To clarify the number of litters in each group.

6. Page 5 Section 8.2

Replace this section with the following:

Males: Daily for 28 days prior to cohabitation, during cohabitation, and following separation of males and females until the day prior to sacrifice (Section 8.8.7).

Females: Daily for 14 days prior to cohabitation, during cohabitation, and continuing through gestation day 6. Sperm negative animals will be dosed until the day prior to sacrifice (Section 8.8.6).

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

Reason: To clarify the frequency of administration of test article.

7. Page 5 Section 8.6

Add the word "distilled" to the 5th and 8th lines of the 1st paragraph to read "deionized distilled water" in both places.

Reason: To clarify that deionized distilled water will be used in the preparation of the 1% methylcellulose/0.2% Tween 80 vehicle.

8. Page 6 Section 8.7

A. Add the following after the 1st sentence: "Within litter cohabitation will not occur because males and females of the same age will arrive approximately 14 days apart."

Reason: A. To indicate that litter mates will not be cohabitated.

9. Page 7 Section 8.8.3

Replace the section for females with the following:

Females: At randomization in week -1 and twice weekly (≈ every 3 - 4 days) during dosing throughout the cohabitation phase. When positive evidence of mating is detected, body weights will be obtained during dosing on gestation days 0 through 6, and in the postdosing period on gestation days 10, 13, and 16.

Reason: To clarify when body weights will be determined for females.

10. Page 7 Section 8.8.4

Replace this section with the following:

Males: During week -1 and twice weekly (≈ every 3 - 4 days), except during cohabitation.

Females: During week -1 and twice weekly (≈ every 3 - 4 days), except during cohabitation. When positive evidence of mating is detected, food consumption will be measured during the following intervals: gestation days 0-3; 3-6; 6-10; 10-13; and 13-16.

Reason: To clarify when food consumption will be determined.

11. Page 7 Section 8.8.5

Replace this section with the following: "Vaginal washings will be performed in all females to monitor the estrous cycle. Washings will be performed in the quarantine period for approximately 10 days prior to randomization. Washings will be performed daily during the dosing period throughout cohabitation until either evidence of copulation is observed or until termination of the cohabitation period."

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

Reason: To clarify when vaginal washings will be performed.

12. Page 7 and 8, Section 8.8.6

Replace this section with the following:

Scheduled Necropsy of Females: Females with evidence of mating (i.e., sperm-positive females) will be euthanized by CO_2 asphyxiation and necropsied on presumed gestation day 16. Sperm-negative females not palpated pregnant will be sacrificed 16 days following the last day of cohabitation. At the discretion of the Study Director, sperm-negative females palpated pregnant may be sacrificed sooner than 16 days after the last day of cohabitation. These occurrences will be documented in the raw data.

At necropsy, the thoracic, abdominal and pelvic cavities will be opened and the viscera examined. Any abnormalities will be recorded. The uterus and ovaries will be removed from the body and examined. For sperm-positive females, uteri with macroscopic implantations will be opened and the number of implantation sites, viable and non-viable fetuses*, and resorptions will be recorded beginning with the distal end of the left uterine horn, noting the position of the cervix, and continuing with the right uterine horn to the distal end. The *corpora lutea* on each ovary will be counted and the number recorded. For sperm-negative, pregnant females, the number of implantation sites and *corpora lutea* will be recorded and used in the calculation of preimplantation loss and mating and fertility indices. Because the end of the dosing period, i.e., gestation day 6, is unknown, the number of viable and non-viable fetuses and resorption sites in these animals will be recorded and retained with the raw data, but will not be utilized in the statistical analysis.

*A viable fetus is defined as one that has pink, well vascularized tissue; a dark red placenta; and clean, reddish amniotic fluid. A non-viable fetus is defined as one that has white, non-vascularized tissue; a necrotic, green placenta; and cloudy, dark amniotic fluid.

Uteri with no macroscopic evidence of implantations will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

The necropsy procedure will include retention of the uterus and ovaries from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparison. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

Reason:

A. To indicate a change in scheduled necropsy from gestation day 13 to gestation day 16.

B. To provide the criterion for determining viability or non-viability of the gestation day 16 fetus.

C. To change the percentage of aqueous ammonium sulfide from 0.5% to 10%.

D. To indicate that *corpora lutea* will be recorded if implantation sites are detected.

E. To indicate, per the ICH guidelines, that the uterus and ovaries and organs/tissues with gross lesions from WR242511 Tartrate-treated females will be saved.

F. To indicate when comparable organs/tissues from control animals will be retained.

13. Page 8 Section 8.8.7

A. In the 1st paragraph, delete "F_0" from the 5th sentence.

B. In the 1st paragraph, delete the 6th sentence: "Gross lesions will be saved at the discretion of the Study Director."

C. Replace the 2nd paragraph with the following:

The necropsy procedure will include retention of both testes in Bouin's fixative, and the left epididymis, prostate, and both seminal vesicles from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparisons. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

Reason: A. Irrelevant to the study.

B. To indicate per the ICH guidelines, that selected reproductive tissues and organs/tissues with gross lesions from WR242511 Tartrate-treated males will be saved.

C. To indicate when comparable organs/tissues from control animals will be retained.

14. Page 9 Section 8.8.8

Replace this section with the following:

Unscheduled Deaths: All animals found dead or euthanized *in extremis* during the study and females that deliver early will be euthanized by CO_2 asphyxiation and grossly examined externally and internally. Body cavities (thoracic, abdominal, and pelvic) will be opened and examined. Uterine contents will be examined and the number of implants will be recorded. The number of *corpora lutea* on each ovary will be noted. Any abnormalities will be recorded. Organs/tissues with gross lesions will be saved in 10% neutral buffered formalin for possible histopathological examination. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

Uteri with no macroscopic evidence of implants will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

Reason:

A. It is not necessary to examine the cranial cavity during necropsy.

B. To indicate that all organs/tissues with gross lesions from WR242511 Tartrate-treated animals will be saved for possible histopathological examination.

C. To change the percentage of aqueous ammonium sulfide from 0.5% to 10%.

D. To indicate that *corpora lutea* will be recorded if implantation sites are detected.

15. Page 9 Section 8.9

A. Add "no. non-viable fetuses" to the 1st sentence in the second paragraph.

B. Move "(C.L.)" in second paragraph to after "no. of *corpora lutea*" in first paragraph.

Reason:

A. To include the number of non-viable fetuses in the statistical analysis of the data.

B. To correct a typographical error.

STUDY DIRECTOR Debra L. Kirchner 11/06/95
Debra L. Kirchner, Ph.D., D.A.B.T. Date

SPONSOR APPROVAL [signature] 11/8/95
George Schieferstein, Ph.D. Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

16. Page 5 Section 8.2

Add the following to the end of the last paragraph in the section: "All animals will receive the control article by gavage for three days during week -1 to acclimate them to the dosing procedure."

Reason: To indicate that all animals were acclimated to the dosing procedure.

17. Page 7 Section 8.8.6

In the second paragraph, change the fourth sentence to read: "For sperm-positive females, uteri with macroscopic implantations will be opened and the number of implantation sites, viable and non-viable fetuses*, and resorptions will be recorded consecutively from the distal end of the left uterine horn to the cervix and then from the distal end of the right uterine horn to the cervix."

Reason: To indicate how these data will be recorded.

STUDY DIRECTOR Debra L Kirchner 12/5/95
Debra L. Kirchner. Ph.D., D.A.B.T. Date

SPONSOR APPROVAL [signature] 12-8-95.
George Schieferstein. Ph.D. Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

18. Page 9 Section 8.9

Replace the first two paragraphs with the following:

Body weights, body weight gains, and calculated daily food consumption will be analyzed by one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

Sperm counts and sperm motility; the numbers of *corpora lutea* (C.L.), implantations, resorptions, viable and nonviable fetuses; and the percent preimplantation loss*, postimplantation loss**, and total implantation loss*** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

Reason: To clarify how the data will be analyzed.

STUDY DIRECTOR Debra L. Kirchner 1/3/96
Debra L. Kirchner, Ph.D., D.A.B.T. Date

SPONSOR APPROVAL George Schieferstein 1/16/96
George Schieferstein, Ph.D. Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

19. Page 5 Section 8.2

A. In the 1st line for males replace "28" with "29".

B. In the 1st line for females replace "14" with "15".

Reason: A. To clarify that males are dosed daily for 29 days prior to cohabitation.

B. To clarify that females are dosed daily for 15 days prior to cohabitation.

20. Page 6 Section 8.7

A. In the 3rd line replace "28" with "29".

B. In the 4th line replace "14" with "15".

Reason: A. To clarify when cohabitation commences for males.

B. To clarify when cohabitation commences for females.

21. Page 9 Section 8.8.7

A. Delete "-60 to -70° C" from the 2nd line of the 1st paragraph and replace with "-70° or less".

B. Add "and the caudal section will be" before "weighed and" in the 3rd line of the 1st paragraph.

C. Delete "Hematoxylin and" from the 5th line of the 1st paragraph.

° D. Add "caudal" before "epididymal samples" and change "1 ml" to "100 uL" in the 6th line of the 1st paragraph.

E. Delete the last sentence of the 1st paragraph and replace with the following: "The results will be reported as total sperm count adjusted for caudal epididymis weight (10^6 sperm/g tissue).

Reason: A. To correctly indicate the temporary storage temperature for the right epididymis.

B. To clarify that caudal section of the epididymides will be weighed and minced.

C. To clarify that the slides will be stained with Eosin.

D. To clarify that the caudal epididymal samples will be homogenized and that a 100 uL sample will be added to the vials.

E. To indicate how the results of the sperm count will be reported.

PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

22. Page 9 Section 8.9

A. Replace the 1st sentence of the 1st paragraph with the following: "Body weights, body weight gains, calculated daily food consumption, and male organ to brain weight ratios will be analyzed by one-way analysis of variance".

B. Add "sperm morphology" after "sperm counts" in the 1st line of the 2nd paragraph.

Reason: A. To indicate how male organ to brain weight rations will be analyzed.

B. To indicate how sperm morphology will be analyzed.

23. Page 10 Section 8.9

Delete the 2nd sentence and replace with the following: "Sperm-negative pregnant females will be included only in the analysis of the mating and fertility indices".

Reason: To clarify that sperm-negative pregnant females will be included only in the analysis of the mating and fertility indices.

STUDY DIRECTOR Debra L Kirchner 3/8/96
Debra L. Kirchner. Ph.D., D.A.B.T. Date

SPONSOR APPROVAL George Schieferstein 3/11/96.
George Schieferstein, Ph.D. Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 197
Title: Oral Fertility and Early Embryonic Development Study of WR242511 Tartrate in Rats

24. Page 9 Section 8.8.7

Add the following sentence to the end of the 1st and 2nd paragraphs: "Sperm samples will be discarded after analysis".

Reason: To indicate the disposition of sperm samples used to assess motility, morphology, and count.

25. Page 10 Section 8.9

Delete the 2nd sentence and replace with the following: "Sperm-negative pregnant females will be included in the analysis of the numbers of *corpora lutea* and implantations, the percent preimplantation loss, and the mating and fertility indices".

Reason: To clarify when data from sperm-negative pregnant females will be used in statistical analysis.

STUDY DIRECTOR Debra L Kirchner 4/22/96

Debra L. Kirchner, Ph.D., D.A.B.T. Date

SPONSOR APPROVAL _____ _____

George Schieferstein, Ph.D. Date

DRAFT

APPENDIX H

STUDY DEVIATIONS

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-16
Study No.: 197

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TOXICITY STUDY OF WR242511 TARTRATE IN RATS

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	Food consumption was not measured for the following: days 1 - 5 for female Nos. 229 and 235 in the 1 mg base/kg/day group (wet feed); days 5 - 8 for male No. 225 in the 1 mg base/kg/day group (technician error); and days 33 - 36 for male No. 153 in the 0.3 mg base/kg/day group (technician error).	None, sufficient data exists to interpret food consumption in these groups.
Protocol	Sperm motility not calculated for male No.259 in the 3 mg base/kg/day group (technician error).	None, sufficient data exists to interpret sperm motility in this group.

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, Illinois, 60612.

The above deviations did not affect the integrity of the study.

Debra L. Kirchner, Ph.D., D.A.B.T.

_____
Date