# Toxicology Research Laboratory

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
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Title Page

Study Report for Task Order No. UIC-12A

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR279396

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

March 24, 1995

Performing Laboratory

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This study evaluated the toxicity of WR279396 (Iowa Formulation 232 containing 15% paromomycin sulfate and 0.5% gentamicin sulfate) in CD® rats following four weeks of daily dermal application. Three groups, each composed of 10 rats/sex, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) were 0.07, 0.33, and 1.67 ml/kg, respectively, in low, mid and high dose animals. This corresponds to doses of 20, 100 and 500 mg/kg/day of paromomycin + 0.7, 3.3, 16.7 mg/kg/day of gentamicin, respectively. A control group of 10 male and 10 female rats received the test article vehicle (WR279396-Placebo, Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Due to the appearance of moderate to severe erythema in mid and high dose animals on days 4 and 5, the volume (amount) of test article or vehicle control article administered was reduced to one-half the initial dose levels beginning on day 6 and for the remainder of the study. On day 6 and thereafter, test article volume (amount) was administered once daily instead of as a split dose twice daily. Following reduction in dosing frequency, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was also observed in several high dose animals and was generally of minimal severity. Except for one mid dose male, these dermal histologic changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.33 or 0.07 ml/kg/day. Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmology evaluations and organ weights were not affected by test article treatment in any of the dose levels tested. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day at lower dosing volumes (*i.e.* 0.33 or 0.07 ml/kg) results in dermal irritation and potentially histologic changes in the skin at the exposure site.

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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 176 entitled "Four Week Toxicity Study of WR279396 after Daily Dermal Application in CD® 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 with the following reservations.

The identity, strength, purity and composition or other characteristics to define the test or control articles have not been determined by the testing facility.

The stability of the test article or control article under the test conditions has not been determined by the testing facility.

Analyses to determine the uniformity, concentration, or stability of the test or control mixtures were not performed by the testing facility.

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

Signature

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

10/3/95
Date

## QUALITY ASSURANCE STATEMENT

STUDY TITLE: FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

STUDY NUMBER: 176

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 10/28/94

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 10/28/94, TO STUDY DIR 10/28/94, TO MGMT 10/28/94
PHASES: PROTOCOL REVIEW

INSPECT ON 2/22/95, TO STUDY DIR 2/24/95, TO MGMT 2/27/95
PHASES: ROOM ENVIRONMENT

INSPECT ON 2/23/95, TO STUDY DIR 2/24/95, TO MGMT 2/27/95
PHASES: DOSING, BODY WEIGHT, FOOD CONSUMPTION AND CLINICAL SIGNS

INSPECT ON 3/23/95, TO STUDY DIR 3/24/95, TO MGMT 3/24/95
PHASES: BLOOD COLLECTION, CLINICAL PATHOLOGY AND MICROCHIP IDENTIFICATION SCANNING

INSPECT ON 4/26-27/95, TO STUDY DIR 4/27/95, TO MGMT 5/1/95
PHASES: RAW DATA

INSPECT ON 6/22-23/95, TO STUDY DIR 6/23/95, TO MGMT 6/23/95
PHASES: PATHOLOGY DRAFT REPORT

INSPECT ON 6/26/95, TO STUDY DIR 6/26/95, TO MGMT 6/27/95
PHASES: DRAFT REPORT

INSPECT ON 10/3/95, TO STUDY DIR 10/3/95, TO MGMT 10/3/95
PHASES: FINAL REPORT

Ronald Rohrbeck 10/3/95

QUALITY ASSURANCE DATE

Signature Page

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Test Article.: WR279396

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

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

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine — 10/3/95

Barry S. Levine, D.Sc., D.A.B.T. — Date
Study Director

Clyde W. Wheeler — 10/3/95

Clyde W. Wheeler, Ph.D. — Date
Toxicologist

Study Initiation: October 28, 1994
Dosing Initiation: February 23, 1995
In-Life Completion: March 24, 1995

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## 1. SUMMARY

This study evaluated the local and systemic (organ) toxicity of WR279396 (Iowa Formulation 232 containing 15% paromomycin sulfate and 0.5% gentamicin sulfate) in CD® rats following four weeks of daily dermal application. The results are summarized in Table 1. Three groups, each composed of 10 male and 10 female rats, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) were 0.07, 0.33, and 1.67 ml/kg, respectively, in low, mid and high dose animals. This corresponds to doses of 20, 100 and 500 mg/kg/day of paromomycin + 0.7, 3.3, 16.7 mg/kg/day of gentamicin, respectively. A control group of 10 male and 10 female rats received the test article vehicle (WR279396-Placebo, Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Due to the appearance of moderate to severe erythema in mid and high dose animals on days 4 and 5, the volume (amount) of test article or vehicle control article administered was reduced to one-half the initial dose levels beginning on day 6 and for the remainder of the study. On day 6 and thereafter, test article volume (amount) was administered once daily in the morning instead of as a split dose twice daily.

Following reduction in dosing frequency, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was also observed in several high dose animals and was generally of minimal severity. Except for one mid dose male, these dermal histologic changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.07 or 0.33 ml/kg/day (dose of 20 and 100 mg/kg/day of paromomycin + 0.7 and 3.3 mg/kg/day of gentamicin, respectively). Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmology evaluations and organ weights were not affected by test article treatment in any of the dose levels tested. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

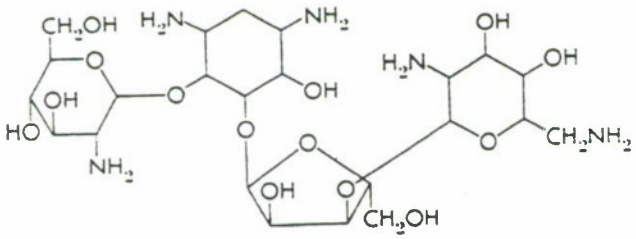
## 2. INTRODUCTION

This study was conducted to determine the local and systemic (organ) toxicity of WR279396 in CD® rats following four weeks of daily dermal application. The study was conducted in accordance with the specifications of the Sponsor as indicated in Task Order UIC-12. The rats used in the study are a standard and accepted rodent species for regulatory toxicology studies, and were specified by the Sponsor. Dermal application is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc., designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on February 23, 1995 and the in-life portion was terminated on March 24, 1995.

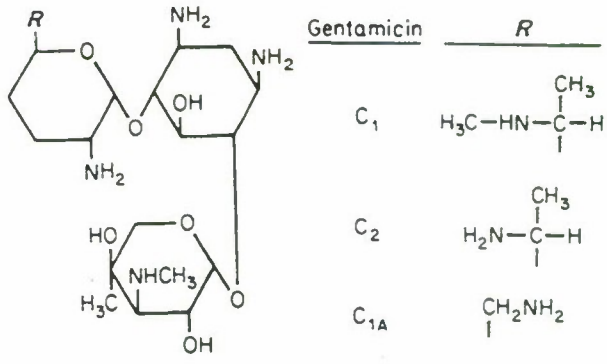
# 3. MATERIALS AND METHODS

## 3.1 Test Article

WR279396 (Bottle No. 42985, Lot No. WRAST02/161), a white cream, was received on January 20, 1995 from Herner & Co., and was assigned an in-house chemical number (1980614). The test article, Iowa Formulation 232 cream, contains 0.5% gentamicin sulfate and 15% paromomycin sulfate. As indicated by the Sponsor, the specific gravity of the test article cream is 1.0. It was stored at 2 to 8°C and ambient humidity, and protected from light in an opaque bottle. The chemical structures of paromomycin and gentamicin are shown below. As illustrated, gentamicin sulfate typically is a mixture of three related sulfate salts isolated from *Micromonospora purpurea*.



Paromomycin




Gentamicin

## 3.2 Placebo (Vehicle)

WR279396-Placebo (Bottle No. 42994, Lot No. WRAST02/162), a white cream, was received on January 20, 1995 from Herner & Co., and was assigned an in-house chemical number (1990614). The control article was Iowa Formulation 232 without gentamicin sulfate and paromomycin sulfate. It was stored at 2 to 8°C and ambient humidity, and protected from light in an opaque bottle.

## 3.3 Animals

Fifty male and fifty female CD® Virus Antibody Free (VAF) rats were obtained from Charles River Breeding Laboratories (Kingston, NY) on February 15, 1995. The animals were approximately 6 weeks old (date of birth January 2, 1995) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a study-unique

quarantine/pretest number following placement in cages. Animals were singly housed in polycarbonate cages with Anderson bed-o-cob® bedding (Heinold, 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 Inc., St. Louis, MO) was provided *ad libitum* from arrival until termination. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. 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 performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.4 Experimental Design

All animals were examined daily during the eight day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Near the end of the quarantine/pretest period, 40 animals of each sex were randomized by sex into four groups shown in the following table using a computer-generated randomization program, stratified on the basis of body weight.

| Treatment Group | Treatment | Paromomycin Dose Level (mg/kg/day) | Gentamicin Dose Level (mg/kg/day) | Dosing Volume (ml/kg/day) | Number of Males | Number of Females |
|---|---|---|---|---|---|---|
| 1 | Vehicle | 0 | 0 | 1.67 x 2 (1.67) | 10 | 10 |
| 2 | WR279396 | 20 (10) | 0.7 (0.04) | 0.07 x 2 (0.07) | 10 | 10 |
| 3 | WR279396 | 100 (50) | 3.3 (1.7) | 0.33 x 2 (0.33) | 10 | 10 |
| 4 | WR279396 | 500 (250) | 16.7 (8.4) | 1.67 x 2 (1.67) | 10 | 10 |

The initial and reduced dose levels were selected following discussions with the Sponsor. The reduced dose levels and dosing volumes (shown inside of parentheses) were chosen based upon the estimated dose which will be given to the patient. As indicated by the Sponsor, the intended routine clinical dose of paromomycin is 5 mg/kg/day. As such, a low dose of 10 mg/kg/day in this study allows for a two-fold margin of safety. It was further stated by the Sponsor that the maximum clinical dose for a severely infected individual would be 50 mg/kg/day. Accordingly, the mid dose (reduced dose level) duplicates this worst case scenario clinical dose. The high dose level in this study of 500 mg/kg/day (1.67 ml WR279396/kg/application) was intended to result in toxicity and was

near the typical upper limit of dermal dosing of 2 ml/kg/application.

Due to the appearance of localized moderate to severe erythema at the treatment site in mid and high animals on days 4 and 5, the dose levels were reduced by one-half after discussions with the Sponsor. Beginning on day 6 and for the remainder of the study, the frequency of treatment was reduced from twice daily to once daily. The dosing volume per application remained constant. The subsequent dose levels of paromomycin sulfate and gentamicin sulfate and the subsequent dosing volumes of test article are shown in the previous page in parentheses.

During the animal selection process, each animal was assigned an animal number unique to it within the population making up the study. This number appeared as an ear tag and was also coded on a subcutaneously implanted microchip. This number also appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, sex, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group.

On days 0 - 5, the test or control article cream was applied by the dermal route twice daily. As previously stated, beginning on day 6 and for the remainder of the study, the frequency of treatment was reduced to once daily. The fur on the back of each test animal was clipped approximately 24 hours prior to initial test article application. An area approximately 7 cm long and extending approximately 3 cm on both sides of the midline was exposed and constituted the dosing area. Only animals with healthy intact skin were used. The backs were reshaved during the course of the study as necessary.

On days -3 to -1, the animals were acclimated to a rodent jacket for dermal application (LOMIR Biomedical Inc., Malone, NY) for 6 - 8 hours each day. The dermal jacket included a plastic shield which extended over, but was not in contact with, the treatment site. Immediately prior to the initial treatment on day 0 and weekly thereafter, the dosing area was abraded by cross-hatched cuts made with a detached size 10 electric clipper blade so that the stratum corneum was penetrated but the dermis was left intact. The test article was administered using a 1 ml tuberculin syringe (0.01 ml graduations) and uniformly applied as a thin film over the exposure area of the skin (up to $\approx$ 10% of the total body surface area). It was applied twice daily on days 0 - 5, in the morning and afternoon, approximately 3 - 4 hours apart, or once daily in the morning beginning on day 6 for at least 28 consecutive days. The specific volume administered (to the nearest 0.01 ml) was adjusted on the basis of each animal's most recent body weight. The material was initially applied to a latex-gloved finger, which was used to uniformly apply the test article to the exposure area of the skin. A separate gloved finger was used for each animal, i.e. after dosing up to four rats, the glove was discarded, and a new latex glove was donned. The application site was left uncovered, however animals were immediately fitted in dermal jackets which prevented them from licking off the material. Approximately 3 - 4 hours after each application (either once daily, or twice daily on days 0 - 5), the exposure site was wiped with a water-moistened paper towel. On days 0 - 5, the test article or control article (vehicle) was applied a second time, as previously

described. Following the final daily application, the animal jackets were removed and left off overnight. The animals were dosed up to and including the day prior to scheduled necropsy on day 28 or 29.

Body weights were recorded at randomization on day -3, on day 0, and weekly thereafter. On days 0 - 5, clinical signs were observed and recorded for all animals twice daily, approximately 1 - 2 hours after each dermal application. The general behavior, posture, locomotion, breathing pattern and coat were observed in all animals. Clinical signs are indicated in the Summary of Clinical Signs (Tables 2.1 and 2.2) and Individual Clinical Signs (Appendix 2) as Clinical Sign 1 or 2, *i.e.* Normal 1st Sign and Normal 2nd Sign. Beginning on day 6, clinical signs were observed and recorded for all animals once daily, approximately 1 - 2 hours after dermal application, and are indicated in Tables 2.1 and 2.2 and Appendix 2 as Clinical Sign 1, *i.e.* Normal 1st Sign. The animals were also observed in the morning for moribundity/mortality. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in week -1, on day 0, and weekly thereafter. Dermal irritation at the treatment site was evaluated on day 0 and weekly thereafter. The draize dermal irritation scoring procedure was employed (Draize, 1965). Food consumption was measured for all animals weekly commencing with week -1.

Hematology and clinical chemistry parameters were measured in all animals on days 27 and 28. The nonfasted animals were anesthetized by inhalation of $CO_2$:$O_2$ (70:30), and approximately 1.5 - 2.0 ml of blood were collected from the orbital sinus to measure the following parameters. The samples were processed in the same random order as collected. Clinical pathology methodology is contained in Appendix 1.

Hematology

- Erythrocyte count and morphology
- Hematocrit
- Hemoglobin
- Leukocyte count, total and differential
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Reticulocyte count

Clinical Chemistry

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Bile acids, total
- Calcium
- Chloride
- Cholesterol
- Creatinine
- Glucose
- Globulin (calc.)
- Phosphorus, inorganic
- Potassium
- Protein, total
- Sodium
- Sorbitol dehydrogenase
- Urea nitrogen (BUN)

With the exception of one accidental death (animal no. 330, low dose male, which was necropsied on the day of its death), all animals were killed and necropsied in random order over a two consecutive day period (days 28 and 29). Animals were anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and then perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin (NBF).

*Adrenal glands
Aorta
*Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Gross lesions
*Heart
Ileum
Jejunum
*Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
*Liver
*Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
*Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic and lumbar)
*Spleen
Sternum with bone marrow
Stomach
*Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

All tissues and organs collected at necropsy were examined microscopically in all control and high dose animals. Because an apparent test article-related lesion was observed in the skin (exposure site) of high dose animals, this tissue and potential target organs of aminoglycosides identified in the protocol (kidneys, ears and sciatic nerve) were histologically evaluated in low and mid dose animals.

### 3.5 Statistical Analyses

For each sex, Analysis of Variance tests was conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis considered weights relative to brain weight. If a significant F ratio was obtained from an ANOVA test ($p \leq 0.05$), Dunnett's t test was used for pair-wise comparisons with the control group.

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

## 4. RESULTS

### 4.1 Mortality and Clinical Signs

Summaries of clinical signs are presented in Tables 2.1 and 2.2. Individual clinical signs are contained in Appendix 2.

Clinical signs of toxicity were not observed during the study, except for dermal irritation at the site of treatment (subsequently discussed). No treatment-related deaths occurred, but one low dose male (animal no. 330) accidently died on day 23. This animal had become extremely intolerant of the restraining jacket (biting, struggling, vocalizing, etc.). On day 23, after being placed in its jacket, the animal freed itself from physical restraint, jumped off the table and landed on the floor. Although it appeared to survive, it convulsed and stopped breathing after it was returned to its cage. Gross necropsy findings of this animal were non-remarkable and no test article-related changes were seen in the kidney, exposure area skin, sciatic nerve and ears.

### 4.2 Dermal Irritation Evaluations

Weekly dermal irritation evaluation (Draize scores) of the treatment sites is presented in Tables 3.1 and 3.2. Representative photographs demonstrating dermal irritation on day 6 are shown in Appendix 10.

On day 4, the twice daily dermal application of the test article resulted in well-defined erythema (draize score of 2) at the exposure site in some mid and high dose animals, and very slight erythema was seen in a few low dose animals. On day 5, moderate to severe erythema (draize score of 3) was seen in the mid and high dose groups. Several low dose animals had well defined erythema. On day 6 (prior to treatment), photographs were taken of the treatment sites in representative animals exhibiting the above-described dermal irritation (Appendix 10). The size of the affected area appeared to correspond to the volume of test article cream applied to the back, however the severity of dermal irritation was not volume dependent. Dermal irritation severity was generally similar in high dose and mid dose animals. Low dose animals had less dermal irritation apparently

because of the very small volume of test article applied. On days 4 and 5, control animals did not exhibit any dermal irritation, and edema formation has not been observed in any animal.

On day 7, after the reduction of WR279396 administration to once daily on day 6, dermal irritation severity greatly diminished from that seen in test article-treated animals on days 4 and 5. Dermal irritation was limited to very slight erythema in mid and high dose animals, except for one high dose male (no. 370) which had well-defined erythema at its exposure site. At that time, several low dose animals also had very slight erythema. On day 14, very slight erythema was observed in all high dose males and most high dose females. Dermal irritation in mid dose animals on day 14 appeared to be a residual effect from the twice daily treatment. At that time, dermal irritation was not observed in low dose animals. By day 21, dermal irritation was limited to the high dose animals, except for a mid dose male and female, and consisted of very slight erythema. On day 27, following three weeks of daily dermal application of WR279396, dermal irritation was generally limited to high dose animals and consisted of very slight erythema (barely perceptible) without edema formation. Very slight erythema was observed in one low dose female and one mid dose male on day 27. The sporadic observation of erythema in these two animals may reflect a greater localization of the test article, *i.e.* greater amount in a small area. Edema formation was not observed during the study.

## 4.3 Body Weights

Summaries of body weights and summaries of weight gains are presented in Tables 4.1 - 4.2 and 5.1 - 5.2, respectively. Individual body weights and weight gains are contained in Appendix 3. In addition, summaries of body weights are graphically depicted in Figures 1 (males) and 2 (females).

Body weights were not affected by WR279396 treatment.

## 4.4 Food Consumption

Summaries of food consumption are presented in Table 6.1 and 6.2. Individual food consumption data are shown in Appendix 4.

Food consumption was not affected by test article treatment. During the last week of treatment, high dose males had a statistically significant increase in mean daily food consumption. This slight increase in food intake was not considered biologically significant.

## 4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Table 7.1 - 7.2. Individual clinical chemistry data are presented in Appendix 5. Summaries of hematological tests are presented in Table 8.1 - 8.2. Individual hematology data are shown in Appendix 6.

Clinical chemistry parameters were not affected by test article treatment. Since neither BUN nor creatinine levels were altered by treatment, overt nephrotoxicity was not apparent. A slight, but statistically significant increase in serum albumin observed in mid dose females on day 28 was not considered biologically significant. At that time, increases in serum albumin levels were not seen in high dose animals or in mid dose males.

Hematology parameters were not affected by WR279396 treatment.

## 4.6 Ophthalmology

The Ophthalmology Report is contained in Appendix 7. WR279396 treatment did not result in treatment-related ophthalmic lesions.

## 4.7 Organ Weights

Organ weight summaries expressed as % brain weight are presented in Table 9.1 - 9.2. Individual organ weight data are contained in Appendix 8.

Organ weights (% brain weight) were not affected by test article treatment. The increase in relative lung weight in mid dose males, but not in high dose animals, was not considered biologically significant. It was apparently due to a slight increase in the absolute lung weights of two mid dose males. This may be an artifact secondary to whole body perfusion.

## 4.8 Pathology

The Pathology Report is contained in Appendix 9. The summary of gross and microscopic lesions is shown in Table 10.

The dermal administration of WR279396 was associated with microscopic changes in the skin exposure area. Acanthosis, consisting of the focal thickening of the epidermis due to a thicker than normal stratum spinosum layer, was observed in 3 of 10 high dose males (mean group severity = 0.30, maximum score = 4.00), 4 of 10 high dose females (mean group severity = 0.50), 1 of 10 mid dose males (mean group severity = 0.10), and 1 of 10 control females (mean group severity = 0.10). These epidermal changes were not observed in mid dose females, low dose animals or control males. Therefore, the minimal to mild acanthosis was considered a test article-related change.

No other histologic changes were considered to be related to WR279396 treatment. Treatment-related changes were not observed in the ears, kidneys or sciatic nerve. Hyperkeratosis was observed more frequently at the skin exposure area than the non-exposure area. This change was characterized by multiple layers of retained keratinized epithelial cells. However, because this dermal change was observed in a similar

frequency in animals treated with the WR279396 vehicle and the high dose of WR279396, it was considered to be a response to the vehicle and/or a response to rubbing during the application and/or removal of the control or test article cream.

## 5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of WR279396 in CD® rats following four weeks of daily dermal application. The results are summarized in Table 1. Dermal application of 1.67 ml/kg/day of WR279396 induced localized, minimal dermal toxicity at the exposure site in high dose animals (500 mg/kg/day of paromomycin + 16.7 mg/kg/day of gentamicin). After four weeks of treatment, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Dermal irritation in mid and low dose animals on days 7 and 14 were considered residual effects of the twice daily treatment on days 0 - 5. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was seen in several high dose animals and was generally of minimal severity in affected animals. Except for one mid dose male, these dermal changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.07 or 0.33 ml/kg/day (doses of 20 and 100 mg/kg/day of paromomycin + 0.7 and 3.3 mg/kg/day of gentamicin, respectively). Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmic evaluations and organ weights were not affected by test article treatment in any of the dose levels tested.

The test article was administered at a constant test article concentration, and the dosing volume of cream was varied. Therefore, if the cream was uniformly spread in a thin monolayer in all treatment groups, one might expect that the size of the affected area may vary, but not the severity of the dermal irritation. However, because the dosing volume of the high dose group was considerably larger compared to that in lower dose groups, the cream was apparently, but unavoidably spread thicker on the backs of high dose animals, especially in centralized areas where dermal irritation was generally observed. Therefore, the localized dermal observed following the once daily application of WR279396 in high dose animals was due to a greater amount of the test article per unit area compared to lower dose groups. Very slight erythema in one mid and low dose animal on day 27 may indicate an uneven application of the test article, producing a greater amount of test article per unit area.

Prior to the reduction in the frequency of dermal applications, dermal irritation was more severe, *i.e.* moderate to severe erythema (draize score = 3). On days 0 - 5, the test and control articles were applied twice, approximately 3 - 4 hours apart, *i.e.* the doses were twice that which were administered on day 6 and thereafter. However, the increased severity in the dermal irritation observed on day 5 (moderate to severe erythema) could not be accounted solely on the basis of increased dose levels of paromomycin and gentamicin. The severity of the dermal irritation significantly and rapidly diminished in all test article-treated groups following the reduction in the frequency of treatment from twice to once daily. By day 21, dermal irritation was generally not observed in mid and low dose animals. Second, high dose animals were still receiving greater amounts of test article on days 6 through the remainder of the study (1.67 ml/kg/day) compared with either mid dose animals (0.33 ml/kg/day x 2) or low dose animals (0.07 ml/kg/day x 2). At these lower total doses of WR279396 per day, greater localized dermal irritation was still observed

in mid dose and low dose animals (moderate to severe erythema and well-defined erythema) compared to that seen in the "new" high dose (very slight erythema). Therefore, the duration of exposure and/or the frequency of test article application (rubbing on and/or removal of the material) appears to significantly affect the localized irritation produced by paromomycin + gentamicin in the Iowa 232 formulation.

In summary, following the single daily dermal administration of WR279396, test article-induced toxicity was limited to minimal dermal toxicity at the treatment site in high dose animals (1.67 ml/kg/day WR279396). No other test article-related changes were observed. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

## 6. PERSONNEL

| | |
|---|---|
| Study Director | Barry S. Levine, D.Sc., D.A.B.T. |
| Toxicologist | Clyde W. Wheeler, Ph.D. |
| Pathologist | Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P. |
| Clinical Veterinarian | James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M. |
| Veterinarian Support | Documented in the raw data |
| Ophthalmologist | Samuel J. Vainisi, D.V.M., D.A.C.V.O. |
| Clinical Laboratory | Maria Lang, A.H.T., C.V.T. |
| Tox. Lab Supervisor | Soudabeh Soura, B.S. |
| Lead Technician | Nancy Dinger, B.S. |
| Quality Assurance | Ronald C. Schoenbeck |

Report preparation was assisted by Dr. Clyde Wheeler, Ms. Soudabeh Soura and Mr. Mukesh Pitroda.

## 7. ARCHIVES

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

## 8. REFERENCE

Draize, J.H. (1965). Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics; Association of Food and Drug Officials of the U.S., (Austin, TX).

Table 1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Toxic Responses

| Treatment | Vehicle (1.67 ml/kg/day)[a] | WR279396 (0.07 ml/kg/day)[a] | WR279396 (0.33 ml/kg/day)[a] | WR279396 (1.67 ml/kg/day)[a] |
|---|---|---|---|---|
| Rats/Sex | 10 | NE | 10 | 10 |
| Deaths[b] | - | 1 (M-AC) | 0 | 0 |
| Clinical Signs | - | NE | NE | NE |
| Dermal Irritation Evaluations[c] | E/E 0M/0F<br>E 0M/0F | E/E 0M/1F<br>E 0M/0F | E/E 1M/0F<br>E 0M/0F | E/E 7M/8F<br>E 0M/0F |
| Body Weights/Gains | - | NE | NE | NE |
| Food Consumption | - | NE | NE | NE |
| Clinical Chemistry | - | NE | NE | NE |
| Hematology | - | NE | NE | NE |
| Ophthalmology | - | NE | NE | NE |
| Organ Weights | - | NE | NE | NE |
| Histopathology | Skin (exposure area) Acanthosis (1F) | NE | Skin (exposure area) Acanthosis (1M) | Skin (exposure area) Acanthosis (3M/4F) |

CONCLUSIONS
Following the single daily dermal administration of WR279396, test article-induced toxicity was limited to minimal dermal toxicity at the treatment site in high dose animals (1.67 ml/kg/day WR279396). This included acanthosis, thickening of the stratum spinosum layer of the epidermis, and barely perceptible erythema. No other test article-related changes were observed. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

[a]On days 0 - 5, animals received twice the volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

[b]AC = accidental death

[c]Dermal evaluations on day 27
E/E = Erythema and Eschar formation
E = edema

NE = No effect

M = Male, F = Female

Table 2.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL SIGNS

STUDY: 176 SEX: MALE

| GROUP: | 1-M | 2-M | 3-M | 4-M |
|---|---|---|---|---|
| Accidental Death | 0 | 1 | 0 | 0 |
| Scheduled Sacrifice | 10 | 9 | 10 | 10 |
| Normal 1st Sign | 10 | 10 | 10 | 10 |
| Normal 2nd Sign | 10 | 10 | 10 | 10 |
| Total Number of Animals | 10 | 10 | 10 | 10 |

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 2.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL SIGNS

STUDY: 176 SEX: FEMALE

| GROUP: | 1-F | 2-F | 3-F | 4-F |
|---|---|---|---|---|
| Scheduled Sacrifice | 10 | 10 | 10 | 10 |
| Normal 1st Sign | 10 | 10 | 10 | 10 |
| Normal 2nd Sign | 10 | 10 | 10 | 10 |
| Total Number of Animals | 10 | 10 | 10 | 10 |

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 3.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Males)

| | | Day 0[a] | | Day 7[a] | | Day 14[a] | | Day 21[a] | | Day 27[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Animal No. | E/E | E | E/E | E | E/E | E | E/E | E | E/E | E |
| Treatment Group 1<br>Vehicle 1.67 ml/kg/day[b] | 301 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 302 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 303 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 304 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 305 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 306 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 307 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 308 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 309 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 310 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment Group 2<br>WR279396 0.07 ml/kg/day[b] | 321 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 322 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 323 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 324 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 325 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 326 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 327 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 328 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 329 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 330 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | c | c |

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.
[c]Accidental death on day 23.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.1 (contd.)

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Males)

| | | Day 0[a] | | Day 7[a] | | Day 14[a] | | Day 21[a] | | Day 27[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Animal No. | E/E | E | E/E | E | E/E | E | E/E | E | E/E | E |
| Treatment Group 3<br>WR279396 0.33 ml/kg/day[b] | 341 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 342 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 343 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 344 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| | 345 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 346 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | 347 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 348 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 349 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 350 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment Group 4<br>WR279396 1.67 ml/kg/day[b] | 361 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 362 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 363 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 364 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 365 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 366 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| | 367 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 368 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | 369 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 370 | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.
[c]Accidental death on day 23.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Females)

| | | Day 0[a] | | Day 7[a] | | Day 14[a] | | Day 21[a] | | Day 27[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Animal No. | E/E | E | E/E | E | E/E | E | E/E | E | E/E | E |
| Treatment Group 1<br>Vehicle 1.67 ml/kg/day[b] | 311 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 312 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 318 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 314 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 315 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 336 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 314 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 318 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 318 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 320 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment Group 2<br>WR279396 0.07 ml/kg/day[b] | 331 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | 332 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 333 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 334 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 335 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 336 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 337 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 338 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 339 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 340 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.2 (contd.)

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Females)

| | | Day 0[a] | | Day 7[a] | | Day 14[a] | | Day 21[a] | | Day 27[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Animal No. | E/E | E | E/E | E | E/E | E | E/E | E | E/E | E |
| Treatment Group 3<br>WR279396 0.33 ml/kg/day[b] | 351 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 357 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | 353 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 355 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 355 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 356 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 357 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 357 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 358 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 360 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment Group 4<br>WR279396 1.67 ml/kg/day[b] | 371 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 372 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 374 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| | 374 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 375 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | 376 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 377 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 378 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| | 379 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | 380 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 4.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

**SUMMARY OF BODY WEIGHTS** (Grams)

STUDY: 176 SEX: MALE

| PERIOD | GROUP: | 1-M | 2-M | 3-M | 4-M |
|---|---|---|---|---|---|
| DAY -3 | MEAN | 248 | 248 | 248 | 248 |
| | S.D. | 6.5 | 6.3 | 7.6 | 6.4 |
| | N | 10 | 10 | 10 | 10 |
| DAY 0 | MEAN | 273 | 270 | 271 | 269 |
| | S.D. | 6.4 | 7.8 | 9.3 | 4.8 |
| | N | 10 | 10 | 10 | 10 |
| DAY 7 | MEAN | 325 | 321 | 325 | 321 |
| | S.D. | 9.4 | 13.5 | 14.1 | 12.2 |
| | N | 10 | 10 | 10 | 10 |
| DAY 14 | MEAN | 363 | 361 | 368 | 365 |
| | S.D. | 14.2 | 17.4 | 20.8 | 21.4 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | MEAN | 393 | 399 | 407 | 399 |
| | S.D. | 17.5 | 20.4 | 26.9 | 27.5 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | MEAN | 418 | 425 | 439 | 431 |
| | S.D. | 23.9 | 19.5 | 29.9 | 29.1 |
| | N | 10 | 9 | 10 | 10 |

Analysis of Variance using DUNNETT'S Procedure

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 4.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

**SUMMARY OF BODY WEIGHTS** (Grams)

STUDY: 176 SEX: FEMALE

| PERIOD | GROUP: | 1-F | 2-F | 3-F | 4-F |
|---|---|---|---|---|---|
| DAY -3 | MEAN | 191 | 191 | 191 | 191 |
| | S.D. | 9.7 | 9.4 | 8.5 | 9.5 |
| | N | 10 | 10 | 10 | 10 |
| DAY 0 | MEAN | 198 | 200 | 198 | 200 |
| | S.D. | 8.3 | 12.1 | 7.9 | 8.8 |
| | N | 10 | 10 | 10 | 10 |
| DAY 7 | MEAN | 223 | 229 | 223 | 228 |
| | S.D. | 9.8 | 14.0 | 12.9 | 11.9 |
| | N | 10 | 10 | 10 | 10 |
| DAY 14 | MEAN | 247 | 255 | 245 | 255 |
| | S.D. | 13.0 | 19.2 | 23.0 | 13.8 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | MEAN | 265 | 276 | 262 | 270 |
| | S.D. | 13.3 | 21.1 | 26.1 | 19.8 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | MEAN | 279 | 289 | 269 | 279 |
| | S.D. | 13.5 | 20.0 | 26.5 | 26.0 |
| | N | 10 | 10 | 10 | 10 |

Analysis of Variance using DUNNETT'S Procedure

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 5.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

**SUMMARY OF WEIGHT GAINS** (Grams)

STUDY: 176 SEX: MALE

| PERIOD[a] | DOSE: (mg/kg) GROUP: | 1-M | 2-M | 3-M | 4-M |
|---|---|---|---|---|---|
| DAY 7[b] | MEAN | 52 | 51 | 54 | 51 |
| | S.D. | 5.5 | 7.6 | 7.6 | 11.6 |
| | N | 10 | 10 | 10 | 10 |
| DAY 14 | MEAN | 38 | 39 | 44 | 44 |
| | S.D. | 7.5 | 6.5 | 8.3 | 10.2 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | MEAN | 30 | 38 | 38 | 34 |
| | S.D. | 9.5 | 5.4 | 7.3 | 8.0 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | MEAN | 25 | 30 | 32 | 32 |
| | S.D. | 7.7 | 2.9 | 8.0 | 5.9 |
| | N | 10 | 9 | 10 | 10 |
| TOTAL GAIN | MEAN | 145 | 156 | 168 | 162 |
| | S.D. | 22.8 | 15.8 | 25.2 | 28.1 |
| | N | 10 | 9 | 10 | 10 |

Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

[b] Baseline is day 0

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 5.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

**SUMMARY OF WEIGHT GAINS** (Grams)

STUDY: 176 SEX: FEMALE

| PERIOD[a] | DOSE: (mg/kg) GROUP: | 1-F | 2-F | 3-F | 4-F |
|---|---|---|---|---|---|
| DAY 7[b] | MEAN | 24 | 28 | 25 | 28 |
| | S.D. | 5.1 | 5.6 | 7.7 | 9.5 |
| | N | 10 | 10 | 10 | 10 |
| DAY 14 | MEAN | 25 | 26 | 22 | 27 |
| | S.D. | 9.6 | 7.2 | 11.3 | 4.9 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | MEAN | 17 | 21 | 17 | 15 |
| | S.D. | 4.4 | 6.8 | 6.3 | 7.4 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | MEAN | 15 | 13 | 8 | 10 |
| | S.D. | 5.5 | 8.6 | 5.7 | 7.6 |
| | N | 10 | 10 | 10 | 10 |
| TOTAL GAIN | MEAN | 81 | 89 | 71 | 80 |
| | S.D. | 14.1 | 12.3 | 22.3 | 23.3 |
| | N | 10 | 10 | 10 | 10 |

Analysis of Variance using DUNNETT'S Procedure

[a]Successive periods

[b]Baseline is day 0

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 6.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

**SUMMARY OF DAILY MEAN FOOD CONSUMPTION** (Grams)

STUDY: 176 SEX: MALE

| PERIOD[a] | GROUP: | 1-M | 2-M | 3-M | 4-M |
|---|---|---|---|---|---|
| DAY 0[b] | INTAKE (g) | 23.4 | 22.8 | 22.7 | 23.0 |
| | S.D. | 0.96 | 0.94 | 1.58 | 1.38 |
| | N | 10 | 10 | 10 | 10 |
| DAY 7 | INTAKE (g) | 26.6 | 26.6 | 26.1 | 26.7 |
| | S.D. | 1.05 | 1.70 | 1.36 | 1.63 |
| | N | 10 | 10 | 9 | 10 |
| DAY 14 | INTAKE (g) | 26.3 | 25.9 | 26.3 | 27.9 |
| | S.D. | 1.46 | 1.86 | 2.16 | 2.50 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | INTAKE (g) | 25.5 | 25.7 | 26.7 | 27.2 |
| | S.D. | 1.57 | 1.76 | 2.33 | 2.51 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | INTAKE (g) | 25.2 | 26.6 | 27.6 | 30.4* |
| | S.D. | 5.04 | 1.70 | 2.27 | 2.31 |
| | N | 10 | 9 | 10 | 10 |

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

[a]Inclusive intervals

[b]Food in on day -6

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 6.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 176 SEX: FEMALE

| PERIOD[a] | GROUP: | 1-F | 2-F | 3-F | 4-F |
|---|---|---|---|---|---|
| DAY 0[b] | INTAKE (g) | 17.1 | 17.3 | 16.9 | 17.0 |
| | S.D. | 1.22 | 1.40 | 1.70 | 1.21 |
| | N | 10 | 10 | 10 | 10 |
| DAY 7 | INTAKE (g) | 20.8 | 20.4 | 19.1 | 20.0 |
| | S.D. | 1.72 | 1.39 | 1.60 | 1.63 |
| | N | 10 | 10 | 10 | 10 |
| DAY 14 | INTAKE (g) | 20.8 | 20.9 | 20.3 | 21.4 |
| | S.D. | 1.15 | 1.74 | 2.86 | 1.66 |
| | N | 10 | 10 | 10 | 10 |
| DAY 21 | INTAKE (g) | 20.1 | 21.0 | 19.9 | 20.0 |
| | S.D. | 1.27 | 1.67 | 3.29 | 2.40 |
| | N | 10 | 10 | 10 | 10 |
| DAY 27 | INTAKE (g) | 23.2 | 22.5 | 20.8 | 22.9 |
| | S.D. | 3.60 | 2.86 | 3.09 | 4.58 |
| | N | 10 | 10 | 10 | 10 |

Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

[b] Food in on day -6

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 7.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL CHEMISTRY TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | ALT | SDH | TP | ALB | GLOB | TBA | ALKP | CHOL |
|---|---|---|---|---|---|---|---|---|
| UNITS: | IU/L | IU/L | g/dL | g/dL | g/dL | umol/L | IU/L | mg/dL |
| Group: 1-M : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 68 | 13.4 | 7.4 | 4.0 | 3.4 | 42.8 | 420 | 65 |
| SD | 20.3 | 3.52 | 0.33 | 0.20 | 0.32 | 19.89 | 100.3 | 12.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-M : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 56 | 12.1 | 7.5 | 4.0 | 3.5 | 40.4 | 371 | 72 |
| SD | 7.7 | 6.02 | 0.36 | 0.27 | 0.35 | 23.37 | 99.4 | 7.7 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Group: 3-M : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 58 | 10.4 | 7.6 | 4.0 | 3.5 | 28.4 | 387 | 67 |
| SD | 9.9 | 3.69 | 0.35 | 0.26 | 0.23 | 15.07 | 92.1 | 7.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-M : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 62 | 9.9 | 7.4 | 4.0 | 3.4 | 30.3 | 369 | 75 |
| SD | 19.3 | 4.82 | 0.44 | 0.28 | 0.35 | 18.03 | 57.9 | 7.7 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL CHEMISTRY TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | BUN | CREAT | NA | K | CL | CA | IP | GLU |
|---|---|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mEq/L | mEq/L | mEq/L | mg/dL | mg/dL | mg/dL |
| Group: 1-M : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 16.3 | 0.55 | 144 | 5.67 | 108 | 10.7 | 9.7 | 155 |
| SD | 1.88 | 0.047 | 1.5 | 0.542 | 3.2 | 0.56 | 0.93 | 26.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-M : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 16.4 | 0.53 | 144 | 5.94 | 106 | 10.8 | 9.3 | 161 |
| SD | 3.29 | 0.048 | 1.1 | 0.827 | 5.7 | 0.52 | 1.08 | 35.1 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Group: 3-M : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 16.5 | 0.55 | 144 | 5.67 | 106 | 10.9 | 9.6 | 158 |
| SD | 1.97 | 0.060 | 1.1 | 0.598 | 3.5 | 0.45 | 0.79 | 34.2 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-M : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 18.5 | 0.54 | 145 | 5.80 | 106 | 11.1 | 9.8 | 173 |
| SD | 2.49 | 0.058 | 2.4 | 1.003 | 4.9 | 0.89 | 1.09 | 41.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 7.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL CHEMISTRY TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | ALT | SDH | TP | ALB | GLOB | TBA | ALKP | CHOL |
|---|---|---|---|---|---|---|---|---|
| UNITS: | IU/L | IU/L | g/dL | g/dL | g/dL | umol/L | IU/L | mg/dL |
| Group: 1-F : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 58 | 12.6 | 7.6 | 4.2 | 3.5 | 25.5 | 234 | 66 |
| SD | 8.5 | 2.98 | 0.52 | 0.31 | 0.43 | 12.65 | 29.1 | 7.5 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-F : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 51 | 13.4 | 7.9 | 4.4 | 3.5 | 19.0 | 238 | 62 |
| SD | 8.8 | 4.35 | 0.54 | 0.24 | 0.56 | 4.39 | 108.7 | 9.2 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 3-F : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 58 | 16.6 | 8.0 | 4.6* | 3.4 | 16.7 | 239 | 64 |
| SD | 12.7 | 3.59 | 0.48 | 0.29 | 0.23 | 2.59 | 76.4 | 8.6 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-F : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 56 | 9.9 | 7.9 | 4.4 | 3.6 | 21.4 | 289 | 72 |
| SD | 16.9 | 4.56 | 0.58 | 0.27 | 0.38 | 4.49 | 71.7 | 11.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*-Significant Difference from Control P < .05

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF CLINICAL CHEMISTRY TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | BUN | CREAT | NA | K | CL | CA | IP | GLU |
|---|---|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mEq/L | mEq/L | mEq/L | mg/dL | mg/dL | mg/dL |
| Group: 1-F : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 16.8 | 0.56 | 143 | 5.61 | 105 | 10.5 | 8.2 | 146 |
| SD | 2.52 | 0.045 | 2.0 | 0.476 | 3.3 | 0.54 | 0.79 | 17.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-F : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 17.1 | 0.53 | 143 | 5.63 | 109 | 10.6 | 8.8 | 163 |
| SD | 2.17 | 0.153 | 1.7 | 0.741 | 5.6 | 0.53 | 1.14 | 17.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 3-F : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 17.5 | 0.60 | 143 | 5.41 | 107 | 11.0 | 8.5 | 155 |
| SD | 1.94 | 0.072 | 1.8 | 0.443 | 3.8 | 0.59 | 1.18 | 35.6 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-F : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 16.0 | 0.55 | 144 | 5.58 | 105 | 10.8 | 7.9 | 153 |
| SD | 1.24 | 0.048 | 1.7 | 0.454 | 2.7 | 0.53 | 1.08 | 20.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 8.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF HEMATOLOGICAL TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | RBC | HGB | HCT | MCV | MCH | MCHC | RETICS | NRBC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | 10^6/mm^3 | g/dL | % | fL | pg | g/dL | % RBCs | COUNT |
| Group: 1-M : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 7.60 | 15.8 | 43.1 | 56.7 | 20.8 | 36.7 | 0.1 | 0 |
| SD | 0.232 | 0.56 | 1.55 | 1.85 | 0.70 | 0.37 | 0.09 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-M : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 7.73 | 15.9 | 43.8 | 56.7 | 20.5 | 36.2 | 0.1 | 0 |
| SD | 0.238 | 0.50 | 1.47 | 2.02 | 0.69 | 0.30 | 0.14 | 0.0 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Group: 3-M : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 7.57 | 15.8 | 43.9 | 58.0 | 21.0 | 36.1 | 0.1 | 0 |
| SD | 0.422 | 0.44 | 1.87 | 2.38 | 0.73 | 1.06 | 0.10 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-M : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 7.68 | 16.3 | 45.0 | 58.6 | 21.3 | 36.4 | 0.2 | 0 |
| SD | 0.420 | 0.74 | 2.09 | 2.75 | 1.08 | 0.40 | 0.15 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## SUMMARY OF HEMATOLOGICAL TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | M. Neutrop | I. Neutrop | Lymphocyte | Monocytes | Eosinophil | Basophils | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 |
| Group: 1-M : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 17.4 | 1.9 | 0.0 | 14.9 | 0.4 | 0.1 | 0.0 | 978 |
| SD | 2.57 | 1.22 | 0.08 | 2.63 | 0.24 | 0.17 | 0.00 | 141.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-M : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 18.2 | 2.2 | 0.0 | 15.4 | 0.5 | 0.1 | 0.0 | 1045 |
| SD | 2.32 | 1.21 | 0.03 | 2.25 | 0.29 | 0.11 | 0.00 | 123.9 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Group: 3-M : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 17.7 | 1.9 | 0.0 | 15.2 | 0.3 | 0.2 | 0.0 | 1006 |
| SD | 4.18 | 0.67 | 0.09 | 4.27 | 0.24 | 0.22 | 0.00 | 89.8 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-M : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 19.0 | 1.9 | 0.1 | 16.6 | 0.4 | 0.0 | 0.0 | 922 |
| SD | 5.91 | 1.79 | 0.08 | 5.91 | 0.18 | 0.06 | 0.00 | 92.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 8.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF HEMATOLOGICAL TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | RBC | HGB | HCT | MCV | MCH | MCHC | RETICS | NRBC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | 10^6/mm^3 | g/dL | % | fL | pg | g/dL | % RBCs | COUNT |
| Group: 1-F : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 7.17 | 15.4 | 41.5 | 57.9 | 21.5 | 37.1 | 0.2 | 0 |
| SD | 0.330 | 0.50 | 1.71 | 1.10 | 0.47 | 0.75 | 0.14 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-F : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 7.17 | 15.7 | 41.8 | 58.3 | 21.9 | 37.5 | 0.2 | 0 |
| SD | 0.455 | 1.05 | 2.56 | 1.61 | 0.56 | 0.54 | 0.24 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 3-F : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 7.22 | 15.6 | 41.6 | 57.7 | 21.6 | 37.4 | 0.2 | 0 |
| SD | 0.233 | 0.52 | 1.31 | 1.32 | 0.68 | 0.75 | 0.12 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-F : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 7.31 | 15.5 | 41.8 | 57.1 | 21.3 | 37.2 | 0.2 | 0 |
| SD | 0.532 | 0.85 | 2.76 | 1.12 | 0.60 | 0.75 | 0.14 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## SUMMARY OF HEMATOLOGICAL TESTS
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | M. Neutrop | I. Neutrop | Lymphocyte | Monocytes | Eosinophil | Basophils | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 | 10^3/mm^3 |
| Group: 1-F : VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 18.1 | 1.9 | 0.0 | 15.6 | 0.4 | 0.1 | 0.0 | 1115 |
| SD | 3.23 | 1.11 | 0.06 | 3.50 | 0.12 | 0.22 | 0.00 | 121.7 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 2-F : WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| MEAN | 15.1 | 1.6 | 0.1 | 13.1 | 0.3 | 0.1 | 0.0 | 1018 |
| SD | 2.98 | 0.98 | 0.11 | 3.06 | 0.24 | 0.09 | 0.00 | 153.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 3-F : WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| MEAN | 15.1 | 1.4 | 0.0 | 13.4 | 0.2 | 0.1 | 0.0 | 986 |
| SD | 2.48 | 0.72 | 0.00 | 2.34 | 0.20 | 0.14 | 0.00 | 130.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Group: 4-F : WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| MEAN | 16.0 | 1.2 | 0.0 | 14.5 | 0.3 | 0.1 | 0.0 | 1101 |
| SD | 5.77 | 0.81 | 0.09 | 5.11 | 0.25 | 0.11 | 0.00 | 94.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 9.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 176
SEX: MALE

ALL FATES DAYS: BEGINNING-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

| GROUP: | | 1-M | 2-M | 3-M | 4-M |
|---|---|---|---|---|---|
| Adrenal Glands(% BRAIN WEIGHT) | | | | | |
| | MEAN | 4.09 | 3.50 | 3.60 | 3.93 |
| | SD | 1.036 | 0.631 | 1.284 | 0.679 |
| | N | 10 | 9 | 10 | 10 |
| Heart(% BRAIN WEIGHT) | | | | | |
| | MEAN | 64.69 | 64.66 | 70.96 | 65.76 |
| | SD | 11.098 | 6.787 | 9.562 | 7.842 |
| | N | 10 | 9 | 10 | 10 |
| Kidneys(% BRAIN WEIGHT) | | | | | |
| | MEAN | 167.04 | 181.04 | 178.74 | 172.86 |
| | SD | 19.892 | 16.523 | 24.644 | 27.576 |
| | N | 10 | 9 | 10 | 10 |
| Liver(% BRAIN WEIGHT) | | | | | |
| | MEAN | 806.73 | 774.09 | 824.03 | 812.25 |
| | SD | 92.081 | 85.503 | 95.493 | 115.787 |
| | N | 10 | 9 | 10 | 10 |
| Lung/Bronchi(% BRAIN WEIGHT) | | | | | |
| | MEAN | 101.76 | 107.67 | 120.37* | 108.90 |
| | SD | 11.155 | 7.546 | 17.975 | 14.516 |
| | N | 10 | 9 | 10 | 10 |
| Spleen(% BRAIN WEIGHT) | | | | | |
| | MEAN | 36.04 | 38.66 | 36.57 | 40.35 |
| | SD | 5.548 | 5.093 | 4.965 | 8.458 |
| | N | 10 | 9 | 10 | 10 |
| Testes(% BRAIN WEIGHT) | | | | | |
| | MEAN | 150.15 | 149.54 | 148.59 | 157.13 |
| | SD | 12.141 | 15.200 | 8.561 | 18.426 |
| | N | 10 | 9 | 10 | 10 |

* - Significant difference P<.05

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 9.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 176
SEX: FEMALE

ALL FATES DAYS: BEGINNING-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

| | GROUP: | 1-F | 2-F | 3-F | 4-F |
|---|---|---|---|---|---|
| Adrenal Glands(% BRAIN WEIGHT) | | | | | |
| | MEAN | 4.23 | 4.70 | 5.05 | 4.73 |
| | SD | 1.194 | 0.518 | 1.122 | 0.985 |
| | N | 10 | 10 | 10 | 10 |
| Heart(% BRAIN WEIGHT) | | | | | |
| | MEAN | 47.98 | 52.12 | 47.81 | 50.04 |
| | SD | 8.199 | 7.105 | 7.213 | 9.551 |
| | N | 10 | 10 | 10 | 10 |
| Kidneys(% BRAIN WEIGHT) | | | | | |
| | MEAN | 121.20 | 133.75 | 130.69 | 131.38 |
| | SD | 20.993 | 19.295 | 20.715 | 15.131 |
| | N | 10 | 10 | 10 | 10 |
| Liver(% BRAIN WEIGHT) | | | | | |
| | MEAN | 551.26 | 577.64 | 568.98 | 567.17 |
| | SD | 76.569 | 57.425 | 87.072 | 66.034 |
| | N | 10 | 10 | 10 | 10 |
| Lung/Bronchi(% BRAIN WEIGHT) | | | | | |
| | MEAN | 92.96 | 89.20 | 91.95 | 92.05 |
| | SD | 24.027 | 12.738 | 13.181 | 7.696 |
| | N | 10 | 10 | 10 | 10 |
| Ovaries(% BRAIN WEIGHT) | | | | | |
| | MEAN | 8.60 | 9.29 | 8.34 | 8.01 |
| | SD | 3.682 | 3.887 | 3.222 | 1.947 |
| | N | 9 | 10 | 10 | 10 |
| Spleen(% BRAIN WEIGHT) | | | | | |
| | MEAN | 34.29 | 32.26 | 31.61 | 31.58 |
| | SD | 7.451 | 5.902 | 4.248 | 6.399 |
| | N | 10 | 10 | 10 | 10 |

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 10

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Microscopic Lesions

| MICROSCOPIC LESIONS[a,b] | | Treatment | | | |
|---|---|---|---|---|---|
| ORGAN - lesion | Sex | Vehicle (1.67 ml/kg/day)[c] | WR279396 (0.07 ml/kg/day)[c] | WR279396 (0.33 ml/kg/day)[c] | WR279396 (1.67 ml/kg/day)[c] |
| SKIN (EXPOSURE AREA) - Acanthosis | M | 0/10 (0.00) | 0/10 (0.00) | 1/10 (0.10) | 3/10 (0.30) |
| | F | 1/10 (0.10) | 0/10 (0.00) | 0/10 (0.00) | 4/10 (0.50) |

[a]Incidences (mean group severity) - Group mean severity was calculated by dividing the sum of all severity scores for a finding by the number of tissues examined.

[b]Lesion severity was scored as follows:

1 = Minimal 3 = Moderate
2 = Mild 4 = Marked

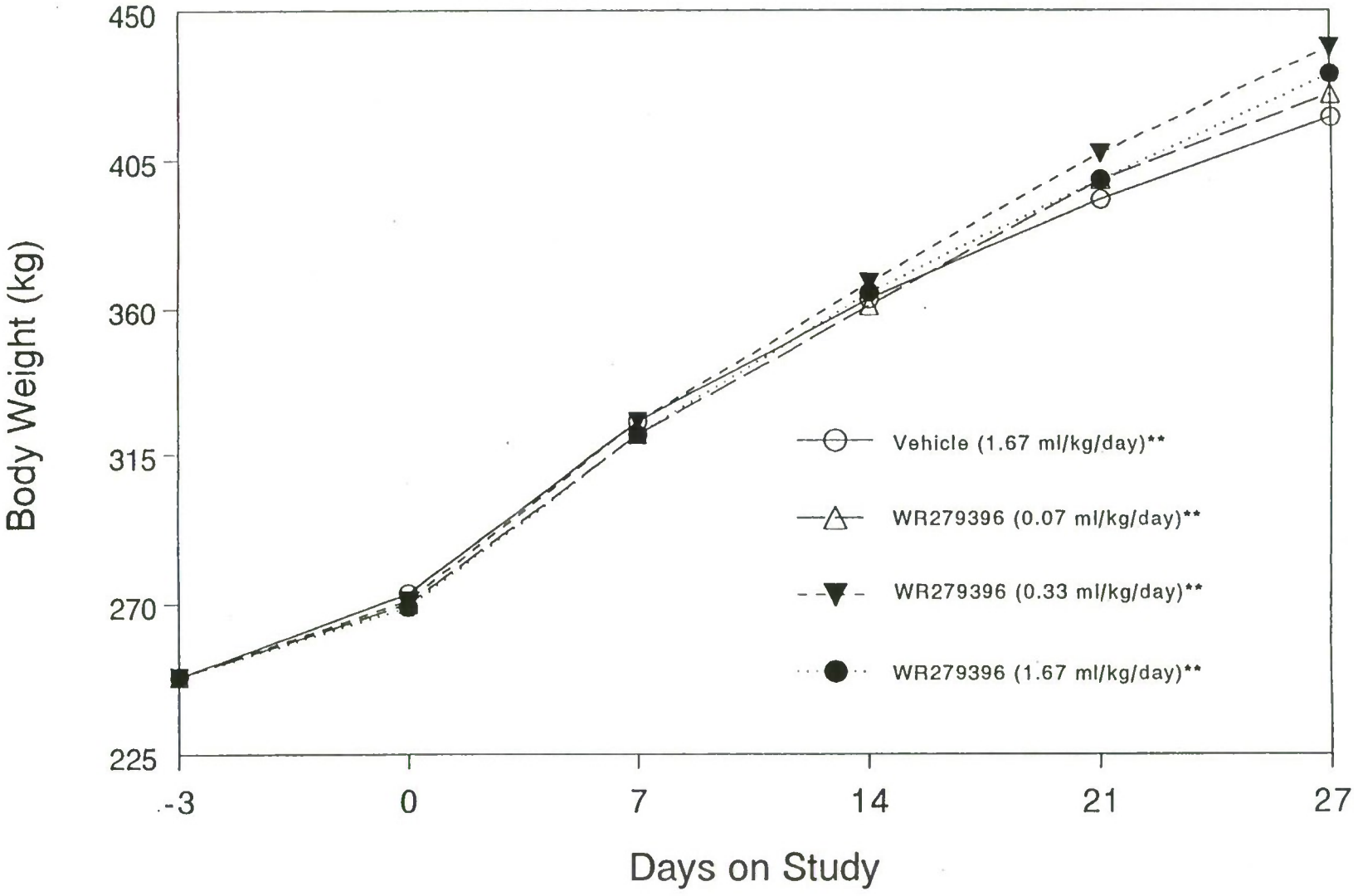
[c]On days 0 - 5, animals received twice the volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

For additional information see Pathology Report in Appendix 9.

# Figure 1

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Male Body Weights



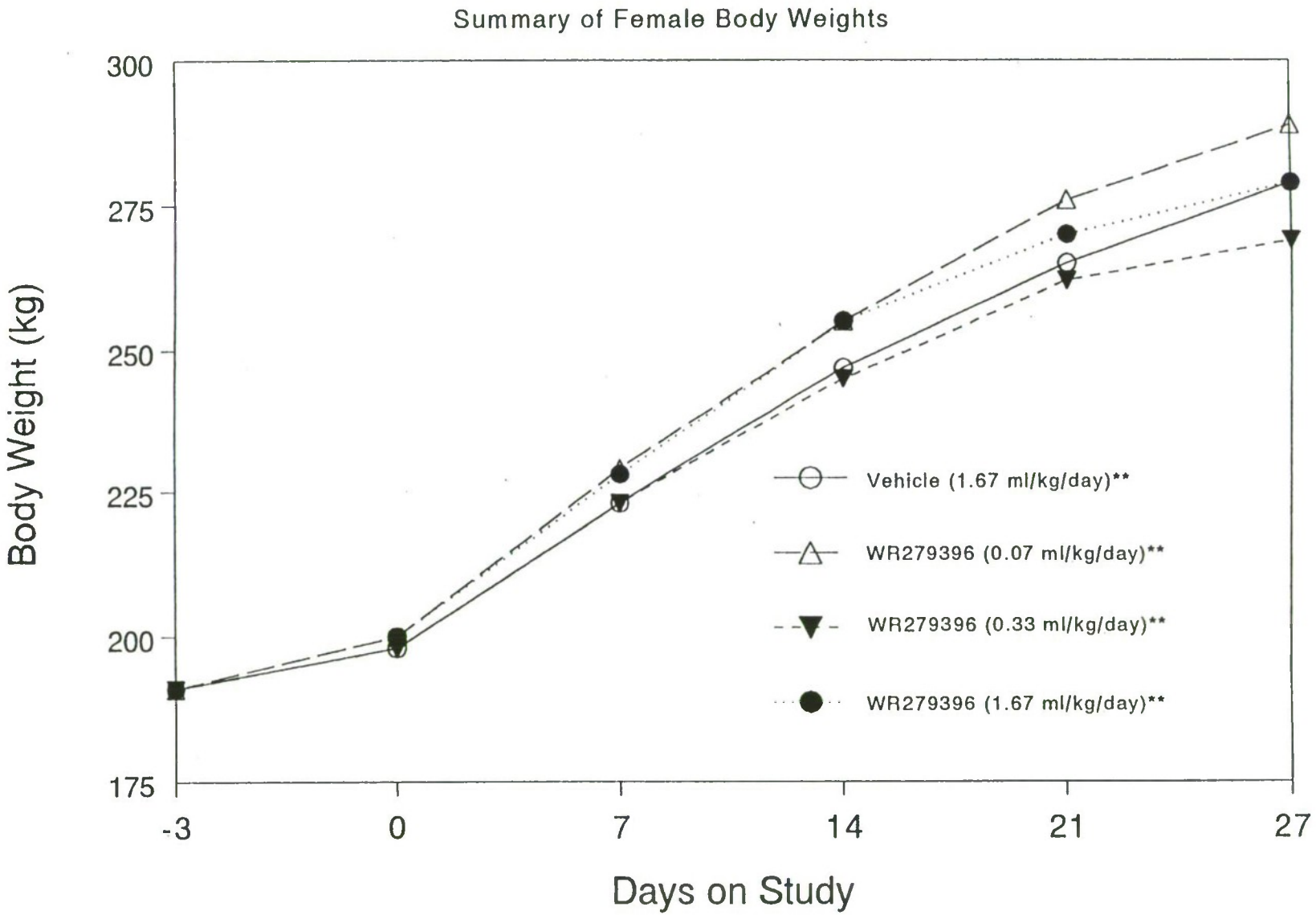

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.



Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study NO.: 176

# Figure 2

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS




**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.



Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study NO.: 176

# APPENDIX 1

# CLINICAL PATHOLOGY METHODOLOGY

## CLINICAL CHEMISTRY

Alanine Aminotransferase (ALT)

Modified Wroblewski & La Due procedure
Ciba-Corning 550 Express Clinical Chemistry System
Henry, R.J., Chiamori, N., Golub, O.J. and Berkman, S.
Am. J. Clin. Path., 34, 381, 1960.

Sorbitol Dehydrogenase (SDH)

Fructose → Sorbitol oxidase reaction
Ciba-Corning 55 Express Clinical Chemistry System
Asada, M. and Galanbos J.T.
Gastroenterology 44, 578, 1963
Wiesner, I.S. *et al.*
Am. J. dig. Dis. 10, 147, 1965.

Total Protein

Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.R.
J. Biol. Chem. 131, 197, 1939.

Albumin

Bromocresol green method
Ciba-Corning 550 Express Clinical Chemistry System
Doumas, B.T. and Biggs, H.G.
Standard Methods of Clinical Chemistry, 7, 175, 1972.

Total Bile Acids

3$\alpha$- Hydroxy bile acid oxidation procedure (Sigma Diagnostic kit)
Ciba-Corning 550 Express Clinical Chemistry System
Mashige, F. *et al.*
Clin. Chem. 27, 1352-1356, 1981.

Alkaline Phosphatase

Modified Bessey-Lowry procedure
Ciba-Corning 550 Express Clinical Chemistry System
Neumann, H. and Von Vreedendaal
M. Clin. Chem. Acta., 17, 183, 1967.

Cholesterol

Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Rosechlow, P., et. al
Z.F. Klin. Chem. V. Klin. Biochem. 12, 226, 1974.

Urea Nitrogen (BUN)

Modified urease technique
Ciba-Corning 550 Express Clinical Chemistry System
Talke, H. and Schubert, G.E.
Klin. Wchnschr. 43, 174, 1965.

Creatinine

Jaffe method
Ciba-Corning 550 Express Clinical Chemistry System
Larsen. K.
Clin. Chem. Acta, 41, 209, 1972

Na+, K+

Ion specific electrodes
Model 614 ISE Na+/K+ Analyzer (Ciba Corning)

Chloride

Mecuric thiocyanate procedure
Ciba-Corning 550 Express Clinical Chemistry System
Zall, O.M., Fisher, D. and Garner, M.Q.
Anal. Chem, 28, 1065, 1956.

Calcium

Modified alizarin procedure
Ciba-Corning 550 Express Clinical Chemistry System
Frings, C.S., et. al.
Clin. Chem., 16, 816, 1970.

Phosphorus, Inorganic

Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Fiske, C.H. and Subbarow, Y.
J. Biol. Chem. 66, 325, 1925.

Glucose

Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Bondar, J.L. and Mead, D.C.
Clin. Chem. 20, 586, 1974.

# HEMATOLOGY

Erythrocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Hemoglobin
Cyanomethemoglobin method
Sysmex K1000 Hematology Analyzer

Hematocrit
Indirect method; calculated value based on volume of red cells and volume of blood

Mean Corpuscular Volume (MCV)
Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)
Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)
Indirect method; calculated value based on hematocrit and hemoglobin

Reticulocyte Count
New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Platelet Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Differential Count
Neutrophils - Immature (bands)
Neutrophils - Mature (segs)
Monocytes
Basophils
Lymphocytes
Eosinophils
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

Nucleated RBCs
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

RBC Morphology
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

# APPENDIX 2

# INDIVIDUAL OBSERVATIONS (CLINICAL SIGNS)

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 1-M SEX: MALE
DAY 0-DAY 29 DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 301 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 302 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 303 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 304 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 305 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 306 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 307 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 308 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 309 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 310 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 2-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 321 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 322 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 323 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 324 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 325 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 326 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 327 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 328 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 329 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 330 | Accidental Death | | | DAY 23 |
| | Normal 1st Sign | | | DAY 0-DAY 22 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 3-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 341 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 342 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 343 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 344 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 345 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 346 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 347 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 348 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 349 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 350 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 4-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 361 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 362 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 363 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 364 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 365 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 366 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 367 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 368 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 369 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 370 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 29 DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 311 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 312 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 313 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 314 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 315 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 316 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 317 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 318 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 319 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 320 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 331 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 332 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 333 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 334 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 335 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 336 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 337 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 338 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 339 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 340 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 351 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 352 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 353 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 354 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 355 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 356 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 357 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 358 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 359 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 360 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 371 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 372 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 373 | Normal 1st Sign | | | DAY 0-DAY 28 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 29 |
| 374 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 375 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 376 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 377 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 378 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 379 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |
| 380 | Normal 1st Sign | | | DAY 0-DAY 27 |
| | Normal 2nd Sign | | | DAY 0-DAY 5 |
| | Scheduled Sacrifice | | | DAY 28 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 3

# INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 301 | 245 | 270 | 318 | 348 | 377 | 394 |
| 302 | 238 | 269 | 329 | 361 | 399 | 421 |
| 303 | 257 | 275 | 319 | 347 | 383 | 411 |
| 304 | 248 | 269 | 316 | 358 | 386 | 412 |
| 305 | 240 | 264 | 315 | 356 | 384 | 407 |
| 306 | 256 | 285 | 345 | 390 | 421 | 456 |
| 307 | 253 | 277 | 331 | 383 | 419 | 454 |
| 308 | 249 | 273 | 321 | 354 | 376 | 403 |
| 309 | 251 | 282 | 333 | 368 | 376 | 386 |
| 310 | 243 | 270 | 326 | 366 | 407 | 437 |
| MEAN | 248 | 273 | 325 | 363 | 393 | 418 |
| S.D. | 6.5 | 6.4 | 9.4 | 14.2 | 17.5 | 23.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 321 | 251 | 275 | 322 | 363 | 395 | 427 |
| 322 | 257 | 280 | 329 | 358 | 387 | 414 |
| 323 | 244 | 264 | 308 | 349 | 385 | 415 |
| 324 | 253 | 278 | 336 | 388 | 430 | 464 |
| 325 | 243 | 264 | 315 | 350 | 387 | 415 |
| 326 | 250 | 275 | 334 | 372 | 419 | 452 |
| 327 | 239 | 255 | 298 | 333 | 373 | 407 |
| 328 | 255 | 271 | 319 | 356 | 395 | 422 |
| 329 | 240 | 265 | 312 | 350 | 384 | 413 |
| 330 | 248 | 273 | 340 | 387 | 430 | a |
| MEAN | 248 | 270 | 321 | 361 | 399 | 425 |
| S.D. | 6.3 | 7.8 | 13.5 | 17.4 | 20.4 | 19.5 |
| N | 10 | 10 | 10 | 10 | 10 | 9 |

--: Data Unavailable a: Accidental Death

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 341 | 258 | 288 | 347 | 404 | 448 | 481 |
| 342 | 248 | 265 | 321 | 363 | 399 | 436 |
| 343 | 247 | 271 | 323 | 361 | 399 | 431 |
| 344 | 245 | 267 | 319 | 356 | 397 | 435 |
| 345 | 243 | 264 | 313 | 357 | 383 | 419 |
| 346 | 243 | 262 | 298 | 329 | 356 | 373 |
| 347 | 232 | 258 | 320 | 368 | 409 | 455 |
| 348 | 256 | 279 | 337 | 374 | 412 | 438 |
| 349 | 253 | 273 | 333 | 379 | 423 | 449 |
| 350 | 252 | 279 | 337 | 392 | 441 | 472 |
| MEAN | 248 | 271 | 325 | 368 | 407 | 439 |
| S.D. | 7.6 | 9.3 | 14.1 | 20.8 | 26.9 | 29.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 361 | 245 | 267 | 326 | 363 | 386 | 419 |
| 362 | 235 | 261 | 318 | 366 | 409 | 435 |
| 363 | 243 | 269 | 320 | 362 | 397 | 433 |
| 364 | 257 | 279 | 330 | 381 | 415 | 455 |
| 365 | 245 | 266 | 306 | 342 | 373 | 406 |
| 366 | 252 | 269 | 309 | 341 | 372 | 398 |
| 367 | 248 | 269 | 332 | 381 | 413 | 435 |
| 368 | 251 | 271 | 300 | 332 | 355 | 390 |
| 369 | 246 | 269 | 333 | 396 | 444 | 483 |
| 370 | 255 | 274 | 333 | 386 | 426 | 459 |
| MEAN | 248 | 269 | 321 | 365 | 399 | 431 |
| S.D. | 6.4 | 4.8 | 12.2 | 21.4 | 27.5 | 29.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 311 | 189 | 197 | 231 | 263 | 284 | 298 |
| 312 | 186 | 193 | 212 | 240 | 257 | 270 |
| 313 | 209 | 215 | 237 | 268 | 281 | 283 |
| 314 | 193 | 203 | 224 | 232 | 251 | 269 |
| 315 | 192 | 200 | 219 | 251 | 270 | 291 |
| 316 | 200 | 205 | 232 | 248 | 257 | 270 |
| 317 | 176 | 187 | 213 | 227 | 242 | 254 |
| 318 | 180 | 188 | 209 | 239 | 263 | 281 |
| 319 | 198 | 200 | 231 | 251 | 266 | 286 |
| 320 | 188 | 195 | 217 | 254 | 275 | 292 |
| MEAN | 191 | 198 | 223 | 247 | 265 | 279 |
| S.D. | 9.7 | 8.3 | 9.8 | 13.0 | 13.3 | 13.5 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 331 | 189 | 193 | 217 | 242 | 260 | 266 |
| 332 | 205 | 220 | 249 | 281 | 304 | 313 |
| 333 | 175 | 182 | 210 | 236 | 258 | 269 |
| 334 | 204 | 209 | 248 | 283 | 318 | 318 |
| 335 | 182 | 188 | 214 | 227 | 250 | 264 |
| 336 | 184 | 196 | 222 | 237 | 263 | 280 |
| 337 | 190 | 197 | 235 | 261 | 280 | 297 |
| 338 | 192 | 201 | 226 | 259 | 277 | 304 |
| 339 | 194 | 200 | 224 | 252 | 273 | 277 |
| 340 | 197 | 217 | 241 | 268 | 276 | 300 |
| MEAN | 191 | 200 | 229 | 255 | 276 | 289 |
| S.D. | 9.4 | 12.1 | 14.0 | 19.2 | 21.1 | 20.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 351 | 191 | 198 | 218 | 232 | 250 | 259 |
| 352 | 199 | 207 | 232 | 260 | 265 | 287 |
| 353 | 206 | 212 | 242 | 267 | 285 | 289 |
| 354 | 187 | 190 | 203 | 207 | 216 | 226 |
| 355 | 183 | 188 | 210 | 229 | 245 | 250 |
| 356 | 186 | 197 | 219 | 231 | 248 | 255 |
| 357 | 194 | 201 | 221 | 244 | 257 | 262 |
| 358 | 193 | 197 | 238 | 283 | 306 | 315 |
| 359 | 176 | 189 | 214 | 233 | 254 | 255 |
| 360 | 195 | 204 | 235 | 265 | 291 | 296 |
| MEAN | 191 | 198 | 223 | 245 | 262 | 269 |
| S.D. | 8.5 | 7.9 | 12.9 | 23.0 | 26.1 | 26.5 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY -3 | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|---|
| 371 | 192 | 206 | 232 | 257 | 264 | 283 |
| 372 | 193 | 206 | 233 | 255 | 274 | 282 |
| 373 | 208 | 211 | 238 | 268 | 285 | 296 |
| 374 | 187 | 194 | 227 | 249 | 266 | 270 |
| 375 | 201 | 213 | 240 | 271 | 289 | 301 |
| 376 | 182 | 187 | 224 | 252 | 265 | 278 |
| 377 | 192 | 197 | 246 | 275 | 307 | 330 |
| 378 | 197 | 198 | 213 | 247 | 257 | 258 |
| 379 | 183 | 193 | 214 | 232 | 239 | 239 |
| 380 | 176 | 192 | 213 | 239 | 251 | 255 |
| MEAN | 191 | 200 | 228 | 255 | 270 | 279 |
| S.D. | 9.5 | 8.8 | 11.9 | 13.8 | 19.8 | 26.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 301 | 48 | 30 | 29 | 17 | 124 |
| 302 | 60 | 32 | 38 | 22 | 152 |
| 303 | 44 | 28 | 36 | 28 | 136 |
| 304 | 47 | 42 | 28 | 26 | 143 |
| 305 | 51 | 41 | 28 | 23 | 143 |
| 306 | 60 | 45 | 31 | 35 | 171 |
| 307 | 54 | 52 | 36 | 35 | 177 |
| 308 | 48 | 33 | 22 | 27 | 130 |
| 309 | 51 | 35 | 8 | 10 | 104 |
| 310 | 56 | 40 | 41 | 30 | 167 |
| MEAN | 52 | 38 | 30 | 25 | 145 |
| S.D. | 5.5 | 7.5 | 9.5 | 7.7 | 22.8 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL WEIGHT GAIN (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 7[c] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 321 | 47 | 41 | 32 | 32 | 152 |
| 322 | 49 | 29 | 29 | 27 | 134 |
| 323 | 44 | 41 | 36 | 30 | 151 |
| 324 | 58 | 52 | 42 | 34 | 186 |
| 325 | 51 | 35 | 37 | 28 | 151 |
| 326 | 59 | 38 | 47 | 33 | 177 |
| 327 | 43 | 35 | 40 | 34 | 152 |
| 328 | 48 | 37 | 39 | 27 | 151 |
| 329 | 47 | 38 | 34 | 29 | 148 |
| 330 | 67 | 47 | 43 | a | -- |
| MEAN | 51 | 39 | 38 | 30 | 156 |
| S.D. | 7.6 | 6.5 | 5.4 | 2.9 | 15.8 |
| N | 10 | 10 | 10 | 9 | 9 |

--: Data Unavailable a: Accidental Death

[b] Successive periods

[c] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 341 | 59 | 57 | 44 | 33 | 193 |
| 342 | 56 | 42 | 36 | 37 | 171 |
| 343 | 52 | 38 | 38 | 32 | 160 |
| 344 | 52 | 37 | 41 | 38 | 168 |
| 345 | 49 | 44 | 26 | 36 | 155 |
| 346 | 36 | 31 | 27 | 17 | 111 |
| 347 | 62 | 48 | 41 | 46 | 197 |
| 348 | 58 | 37 | 38 | 26 | 159 |
| 349 | 60 | 46 | 44 | 26 | 176 |
| 350 | 58 | 55 | 49 | 31 | 193 |
| MEAN | 54 | 44 | 38 | 32 | 168 |
| S.D. | 7.6 | 8.3 | 7.3 | 8.0 | 25.2 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 361 | 59 | 37 | 23 | 33 | 152 |
| 362 | 57 | 48 | 43 | 26 | 174 |
| 363 | 51 | 42 | 35 | 36 | 164 |
| 364 | 51 | 51 | 34 | 40 | 176 |
| 365 | 40 | 36 | 31 | 33 | 140 |
| 366 | 40 | 32 | 31 | 26 | 129 |
| 367 | 63 | 49 | 32 | 22 | 166 |
| 368 | 29 | 32 | 23 | 35 | 119 |
| 369 | 64 | 63 | 48 | 39 | 214 |
| 370 | 59 | 53 | 40 | 33 | 185 |
| MEAN | 51 | 44 | 34 | 32 | 162 |
| S.D. | 11.6 | 10.2 | 8.0 | 5.9 | 28.1 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 311 | 34 | 32 | 21 | 14 | 101 |
| 312 | 19 | 28 | 17 | 13 | 77 |
| 313 | 22 | 31 | 13 | 2 | 68 |
| 314 | 21 | 8 | 19 | 18 | 66 |
| 315 | 19 | 32 | 19 | 21 | 91 |
| 316 | 27 | 16 | 9 | 13 | 65 |
| 317 | 26 | 14 | 15 | 12 | 67 |
| 318 | 21 | 30 | 24 | 18 | 93 |
| 319 | 31 | 20 | 15 | 20 | 86 |
| 320 | 22 | 37 | 21 | 17 | 97 |
| MEAN | 24 | 25 | 17 | 15 | 81 |
| S.D. | 5.1 | 9.6 | 4.4 | 5.5 | 14.1 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 331 | 24 | 25 | 18 | 6 | 73 |
| 332 | 29 | 32 | 23 | 9 | 93 |
| 333 | 28 | 26 | 22 | 11 | 87 |
| 334 | 39 | 35 | 35 | 0 | 109 |
| 335 | 26 | 13 | 23 | 14 | 76 |
| 336 | 26 | 15 | 26 | 17 | 84 |
| 337 | 38 | 26 | 19 | 17 | 100 |
| 338 | 25 | 33 | 18 | 27 | 103 |
| 339 | 24 | 28 | 21 | 4 | 77 |
| 340 | 24 | 27 | 8 | 24 | 83 |
| MEAN | 28 | 26 | 21 | 13 | 89 |
| S.D. | 5.6 | 7.2 | 6.8 | 8.6 | 12.3 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 351 | 20 | 14 | 18 | 9 | 61 |
| 352 | 25 | 28 | 5 | 22 | 80 |
| 353 | 30 | 25 | 18 | 4 | 77 |
| 354 | 13 | 4 | 9 | 10 | 36 |
| 355 | 22 | 19 | 16 | 5 | 62 |
| 356 | 22 | 12 | 17 | 7 | 58 |
| 357 | 20 | 23 | 13 | 5 | 61 |
| 358 | 41 | 45 | 23 | 9 | 118 |
| 359 | 25 | 19 | 21 | 1 | 66 |
| 360 | 31 | 30 | 26 | 5 | 92 |
| MEAN | 25 | 22 | 17 | 8 | 71 |
| S.D. | 7.7 | 11.3 | 6.3 | 5.7 | 22.3 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 7[b] | DAY 14 | DAY 21 | DAY 27 | TOTAL GAIN |
|---|---|---|---|---|---|
| 371 | 26 | 25 | 7 | 19 | 77 |
| 372 | 27 | 22 | 19 | 8 | 76 |
| 373 | 27 | 30 | 17 | 11 | 85 |
| 374 | 33 | 22 | 17 | 4 | 76 |
| 375 | 27 | 31 | 18 | 12 | 88 |
| 376 | 37 | 28 | 13 | 13 | 91 |
| 377 | 49 | 29 | 32 | 23 | 133 |
| 378 | 15 | 34 | 10 | 1 | 60 |
| 379 | 21 | 18 | 7 | 0 | 46 |
| 380 | 21 | 26 | 12 | 4 | 63 |
| MEAN | 28 | 27 | 15 | 10 | 80 |
| S.D. | 9.5 | 4.9 | 7.4 | 7.6 | 23.3 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 4

# INDIVIDUAL FOOD CONSUMPTION DATA

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE:[b] Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 301 | 23 | 26 | 24 | 23 | 27 |
| 302 | 23 | 27 | 28 | 27 | 27 |
| 303 | 23 | 26 | 25 | 25 | 26 |
| 304 | 22 | 24 | 25 | 24 | 25 |
| 305 | 25 | 28 | 27 | 26 | 25 |
| 306 | 24 | 28 | 28 | 27 | 29 |
| 307 | 23 | 27 | 28 | 27 | 28 |
| 308 | 25 | 27 | 27 | 26 | 27 |
| 309 | 23 | 27 | 26 | 23 | 11 |
| 310 | 22 | 26 | 25 | 26 | 26 |
| MEAN | 23 | 27 | 26 | 25 | 25 |
| S.D. | 1.1 | 1.2 | 1.5 | 1.6 | 5.1 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 0 [c] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 321 | 24 | 27 | 26 | 26 | 27 |
| 322 | 23 | 26 | 25 | 24 | 25 |
| 323 | 22 | 24 | 24 | 24 | 25 |
| 324 | 25 | 29 | 29 | 28 | 29 |
| 325 | 23 | 26 | 26 | 25 | 26 |
| 326 | 23 | 28 | 27 | 28 | 28 |
| 327 | 22 | 24 | 23 | 24 | 25 |
| 328 | 22 | 26 | 26 | 25 | 27 |
| 329 | 23 | 27 | 25 | 25 | 28 |
| 330 | 23 | 29 | 28 | 28 | a |
| MEAN | 23 | 27 | 26 | 26 | 27 |
| S.D. | 0.9 | 1.8 | 1.8 | 1.7 | 1.5 |
| N | 10 | 10 | 10 | 10 | 9 |

--: Data Unavailable a: Accidental Death

[b] Inclusive intervals

[c] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 341 | 25 | -- | 29 | 29 | 29 |
| 342 | 21 | 25 | 26 | 25 | 27 |
| 343 | 21 | 27 | 25 | 27 | 27 |
| 344 | 22 | 26 | 24 | 25 | 25 |
| 345 | 22 | 26 | 25 | 26 | 29 |
| 346 | 23 | 24 | 23 | 23 | 23 |
| 347 | 21 | 25 | 26 | 27 | 28 |
| 348 | 24 | 27 | 27 | 28 | 30 |
| 349 | 23 | 27 | 28 | 28 | 27 |
| 350 | 26 | 28 | 30 | 31 | 31 |
| MEAN | 23 | 26 | 26 | 27 | 28 |
| S.D. | 1.8 | 1.3 | 2.2 | 2.3 | 2.4 |
| N | 10 | 9 | 10 | 10 | 10 |

--: Data Unavailable

[a]Inclusive intervals

[b]Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 361 | 22 | 26 | 26 | 25 | 28 |
| 362 | 21 | 27 | 30 | 29 | 30 |
| 363 | 23 | 27 | 29 | 28 | 31 |
| 364 | 24 | 28 | 28 | 28 | 30 |
| 365 | 23 | 26 | 26 | 25 | 29 |
| 366 | 24 | 26 | 24 | 25 | 32 |
| 367 | 26 | 29 | 29 | 28 | 29 |
| 368 | 23 | 23 | 24 | 23 | 27 |
| 369 | 23 | 27 | 31 | 31 | 34 |
| 370 | 23 | 29 | 31 | 30 | 33 |
| MEAN | 23 | 27 | 28 | 27 | 30 |
| S.D. | 1.3 | 1.8 | 2.7 | 2.6 | 2.2 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 0 [b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 311 | 17 | 21 | 21 | 21 | 23 |
| 312 | 16 | 19 | 20 | 19 | 23 |
| 313 | 18 | 20 | 21 | 19 | 19 |
| 314 | 19 | 22 | 21 | 20 | 24 |
| 315 | 17 | 20 | 20 | 20 | 28 |
| 316 | 18 | 21 | 22 | 19 | 20 |
| 317 | 15 | 20 | 20 | 20 | 21 |
| 318 | 18 | 25 | 23 | 22 | 31 |
| 319 | 16 | 20 | 19 | 19 | 20 |
| 320 | 17 | 20 | 22 | 21 | 24 |
| MEAN | 17 | 21 | 21 | 20 | 23 |
| S.D. | 1.2 | 1.7 | 1.2 | 1.1 | 3.8 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 331 | 17 | 21 | 20 | 20 | 26 |
| 332 | 19 | 22 | 23 | 21 | 22 |
| 333 | 16 | 18 | 19 | 20 | 21 |
| 334 | 20 | 22 | 23 | 24 | 22 |
| 335 | 16 | 19 | 19 | 20 | 19 |
| 336 | 16 | 19 | 18 | 20 | 21 |
| 337 | 17 | 22 | 21 | 24 | 28 |
| 338 | 17 | 21 | 22 | 21 | 25 |
| 339 | 17 | 20 | 20 | 19 | 22 |
| 340 | 18 | 20 | 22 | 21 | 21 |
| MEAN | 17 | 20 | 21 | 21 | 23 |
| S.D. | 1.3 | 1.4 | 1.8 | 1.7 | 2.8 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 351 | 17 | 19 | 19 | 19 | 22 |
| 352 | 18 | 21 | 21 | 20 | 25 |
| 353 | 19 | 20 | 22 | 21 | 20 |
| 354 | 14 | 16 | 15 | 15 | 16 |
| 355 | 16 | 18 | 20 | 18 | 18 |
| 356 | 16 | 18 | 19 | 18 | 18 |
| 357 | 17 | 19 | 20 | 19 | 19 |
| 358 | 19 | 21 | 26 | 27 | 24 |
| 359 | 15 | 18 | 19 | 19 | 20 |
| 360 | 18 | 21 | 23 | 24 | 26 |
| MEAN | 17 | 19 | 20 | 20 | 21 |
| S.D. | 1.7 | 1.7 | 2.9 | 3.4 | 3.3 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 0 [b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 371 | 18 | 20 | 21 | 19 | 22 |
| 372 | 18 | 20 | 22 | 21 | 23 |
| 373 | 18 | 20 | 23 | 21 | 23 |
| 374 | 16 | 20 | 20 | 19 | 22 |
| 375 | 19 | 21 | 23 | 21 | 29 |
| 376 | 16 | 19 | 20 | 19 | 20 |
| 377 | 18 | 24 | 25 | 26 | 33 |
| 378 | 16 | 18 | 20 | 18 | 19 |
| 379 | 16 | 19 | 20 | 18 | 21 |
| 380 | 16 | 19 | 20 | 18 | 19 |
| MEAN | 17 | 20 | 21 | 20 | 23 |
| S.D. | 1.2 | 1.6 | 1.8 | 2.4 | 4.5 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE:[b] Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 301 | 139 | 183 | 169 | 164 | 163 |
| 302 | 137 | 188 | 194 | 188 | 163 |
| 303 | 139 | 181 | 175 | 175 | 154 |
| 304 | 132 | 171 | 177 | 166 | 152 |
| 305 | 149 | 197 | 188 | 184 | 148 |
| 306 | 143 | 193 | 199 | 191 | 175 |
| 307 | 140 | 188 | 196 | 192 | 165 |
| 308 | 150 | 191 | 189 | 180 | 164 |
| 309 | 140 | 190 | 181 | 163 | 68 |
| 310 | 134 | 183 | 176 | 179 | 158 |
| MEAN | 140 | 187 | 184 | 178 | 151 |
| S.D. | 5.8 | 7.3 | 10.2 | 11.0 | 30.2 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 0[c] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 321 | 141 | 188 | 181 | 181 | 164 |
| 322 | 136 | 183 | 173 | 169 | 147 |
| 323 | 132 | 168 | 166 | 168 | 149 |
| 324 | 150 | 200 | 202 | 199 | 175 |
| 325 | 135 | 181 | 183 | 175 | 154 |
| 326 | 138 | 195 | 190 | 193 | 169 |
| 327 | 132 | 169 | 162 | 168 | 149 |
| 328 | 130 | 181 | 182 | 173 | 163 |
| 329 | 138 | 192 | 175 | 176 | 166 |
| 330 | 137 | 202 | 198 | 198 | a |
| MEAN | 137 | 186 | 181 | 180 | 160 |
| S.D. | 5.7 | 11.8 | 12.9 | 12.3 | 10.1 |
| N | 10 | 10 | 10 | 10 | 9 |

--: Data Unavailable a: Accidental Death

[b] Inclusive intervals

[c] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 0 [b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 341 | 150 | -- | 206 | 200 | 174 |
| 342 | 127 | 174 | 184 | 174 | 163 |
| 343 | 128 | 188 | 176 | 186 | 162 |
| 344 | 130 | 181 | 171 | 172 | 152 |
| 345 | 131 | 179 | 173 | 179 | 174 |
| 346 | 135 | 165 | 162 | 158 | 138 |
| 347 | 128 | 178 | 180 | 188 | 167 |
| 348 | 143 | 191 | 186 | 196 | 181 |
| 349 | 137 | 188 | 195 | 196 | 163 |
| 350 | 153 | 196 | 208 | 215 | 183 |
| MEAN | 136 | 182 | 184 | 186 | 166 |
| S.D. | 9.5 | 9.5 | 15.1 | 16.4 | 13.6 |
| N | 10 | 9 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 361 | 132 | 181 | 185 | 175 | 165 |
| 362 | 125 | 188 | 210 | 204 | 182 |
| 363 | 136 | 191 | 201 | 196 | 188 |
| 364 | 144 | 193 | 195 | 199 | 181 |
| 365 | 137 | 179 | 184 | 177 | 175 |
| 366 | 146 | 182 | 170 | 176 | 190 |
| 367 | 155 | 202 | 206 | 193 | 175 |
| 368 | 135 | 163 | 169 | 160 | 161 |
| 369 | 135 | 188 | 217 | 214 | 204 |
| 370 | 135 | 201 | 214 | 210 | 200 |
| MEAN | 138 | 187 | 195 | 190 | 182 |
| S.D. | 8.3 | 11.4 | 17.5 | 17.6 | 13.9 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

| ANIMAL # | DAY 0 [b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 311 | 104 | 150 | 150 | 149 | 139 |
| 312 | 95 | 134 | 137 | 134 | 136 |
| 313 | 109 | 141 | 148 | 133 | 116 |
| 314 | 116 | 151 | 146 | 143 | 142 |
| 315 | 99 | 143 | 140 | 139 | 166 |
| 316 | 106 | 147 | 151 | 131 | 120 |
| 317 | 91 | 137 | 141 | 140 | 126 |
| 318 | 106 | 176 | 160 | 156 | 184 |
| 319 | 97 | 140 | 133 | 130 | 121 |
| 320 | 101 | 137 | 151 | 150 | 143 |
| MEAN | 102 | 146 | 146 | 141 | 139 |
| S.D. | 7.3 | 12.1 | 8.0 | 8.9 | 21.5 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

| ANIMAL # | DAY 0 [b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 331 | 100 | 147 | 143 | 142 | 158 |
| 332 | 114 | 153 | 162 | 144 | 132 |
| 333 | 96 | 129 | 134 | 139 | 124 |
| 334 | 121 | 153 | 163 | 170 | 129 |
| 335 | 97 | 131 | 135 | 138 | 112 |
| 336 | 96 | 131 | 126 | 141 | 123 |
| 337 | 100 | 151 | 149 | 165 | 167 |
| 338 | 103 | 149 | 155 | 148 | 148 |
| 339 | 102 | 137 | 143 | 135 | 129 |
| 340 | 110 | 143 | 151 | 144 | 126 |
| MEAN | 104 | 142 | 146 | 147 | 135 |
| S.D. | 8.4 | 9.6 | 12.2 | 11.6 | 17.2 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

| ANIMAL # | DAY 0[b] | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 351 | 102 | 130 | 134 | 136 | 129 |
| 352 | 107 | 146 | 146 | 137 | 148 |
| 353 | 115 | 140 | 156 | 144 | 119 |
| 354 | 82 | 113 | 106 | 107 | 98 |
| 355 | 97 | 128 | 139 | 124 | 110 |
| 356 | 97 | 127 | 131 | 123 | 110 |
| 357 | 99 | 135 | 137 | 133 | 115 |
| 358 | 115 | 148 | 180 | 189 | 145 |
| 359 | 91 | 125 | 131 | 135 | 121 |
| 360 | 105 | 145 | 159 | 165 | 153 |
| MEAN | 101 | 134 | 142 | 139 | 125 |
| S.D. | 10.2 | 11.2 | 19.9 | 23.0 | 18.4 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE:[b] WR279396 (1.67 ml/kg/day)**

| ANIMAL # | DAY 0 | DAY 7 | DAY 14 | DAY 21 | DAY 27 |
|---|---|---|---|---|---|
| 371 | 105 | 139 | 149 | 133 | 131 |
| 372 | 107 | 142 | 152 | 144 | 136 |
| 373 | 107 | 140 | 160 | 148 | 139 |
| 374 | 97 | 138 | 142 | 136 | 130 |
| 375 | 113 | 146 | 158 | 150 | 171 |
| 376 | 95 | 133 | 143 | 135 | 119 |
| 377 | 110 | 167 | 175 | 179 | 199 |
| 378 | 94 | 125 | 141 | 124 | 112 |
| 379 | 95 | 133 | 140 | 125 | 125 |
| 380 | 95 | 132 | 139 | 124 | 113 |
| MEAN | 102 | 140 | 150 | 140 | 138 |
| S.D. | 7.3 | 11.3 | 11.6 | 16.8 | 27.4 |
| N | 10 | 10 | 10 | 10 | 10 |

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 5

# INDIVIDUAL CLINICAL CHEMISTRY DATA

## Clinical Chemistry Test Directory

STUDY: UIC-12A

| NO. | ABBR. / UNITS | DESCRIPTION / PRECISION | CALCULATED | OPERAND A | OPERAND B | ---LOWER LIMIT--- MALE | ---LOWER LIMIT--- FEMALE | ---UPPER LIMIT--- MALE | ---UPPER LIMIT--- FEMALE |
|---|---|---|---|---|---|---|---|---|---|
| 1. | ALT | Alanine Aminotransferase | | | | | | | |
| | IU/L | Integer | NO | | | 30 | 30 | 70 | 70 |
| 2. | SDH | Sorbitol Dehydrogenase | | | | | | | |
| | IU/L | 0.0 | NO | | | 10 | 10 | 30 | 30 |
| 3. | TP | Total Protein | | | | | | | |
| | g/dL | 0.0 | NO | | | 6.0 | 6.0 | 9.5 | 9.5 |
| 4. | ALB | Albumin | | | | | | | |
| | g/dL | 0.0 | NO | | | 3.4 | 3.4 | 5.6 | 5.6 |
| 5. | TBA | Total Bile Acids | | | | | | | |
| | umol/L | 0.0 | NO | | | 25.0 | 25.0 | 75.0 | 75.0 |
| 6. | ALKP | Alkaline Phosphatase | | | | | | | |
| | IU/L | Integer | NO | | | 60 | 40 | 500 | 250 |
| 7. | CHOL | Cholesterol | | | | | | | |
| | mg/dL | Integer | NO | | | 25 | 25 | 75 | 75 |
| 8. | BUN | Blood Urea Nitrogen | | | | | | | |
| | mg/dL | 0.0 | NO | | | 12.0 | 12.0 | 22.0 | 22.0 |
| 9. | CREAT | Creatinine | | | | | | | |
| | mg/dL | 0.00 | NO | | | 0.40 | 0.40 | 0.80 | 0.80 |
| 10. | NA | Sodium | | | | | | | |
| | mEq/L | Integer | NO | | | 140 | 140 | 148 | 148 |
| 11. | K | Potassium | | | | | | | |
| | mEq/L | 0.00 | NO | | | 5.00 | 5.00 | 7.00 | 7.00 |
| 12. | CL | Chloride | | | | | | | |
| | mEq/L | Integer | NO | | | 95 | 95 | 115 | 115 |
| 13. | CA | Calcium | | | | | | | |
| | mg/dL | 0.0 | NO | | | 9.0 | 9.0 | 12.0 | 12.0 |
| 14. | IP | Inorganic Phosphorus | | | | | | | |
| | mg/dL | 0.0 | NO | | | 5.5 | 5.5 | 11.0 | 11.0 |
| 15. | GLU | Glucose | | | | | | | |
| | mg/dL | Integer | NO | | | 80 | 80 | 175 | 175 |
| 16. | GLOB | Globulin | | | | | | | |
| | g/dL | 0.0 | Operand A - Operand B | TP | ALB | 2.5 | 2.5 | 5.0 | 5.0 |

(END OF REPORT)

08-JUN-1995

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

| Animal ID | ALT IU/L | SDH IU/L | TP g/dL | ALB g/dL | GLOB g/dL | TBA umol/L | ALKP IU/L | CHOL mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 301 | 59 | 12.4 | 7.6 | 4.0 | 3.6 | 19.3 | 479 | 72 |
| 302 | 64 | 7.2 | 7.6 | 4.0 | 3.6 | 63.2 | 336 | 60 |
| 303 | 52 | 14.6 | 7.0 | 4.0 | 3.0 | 49.9 | 279 | 81 |
| 304 | 61 | 14.8 | 7.5 | 4.3 | 3.2 | 83.5 | 426 | 59 |
| 305 | 54 | 20.3 | 7.7 | 4.0 | 3.7 | 31.7 | 435 | 47 |
| 306 | 68 | 11.3 | 7.8 | 4.0 | 3.8 | 23.0 | 554 | 77 |
| 307 | 97 | 11.1 | 7.6 | 4.3 | 3.3 | 48.7 | 535 | 65 |
| 308 | 62 | 14.2 | 7.5 | 3.7 | 3.8 | 24.7 | 413 | 70 |
| 309 | 113 | 16.4 | 6.9 | 3.7 | 3.2 | 40.1 | 262 | 75 |
| 310 | 53 | 12.1 | 7.0 | 4.0 | 3.0 | 43.9 | 481 | 42 |
| MEAN | 68 | 13.4 | 7.4 | 4.0 | 3.4 | 42.8 | 420 | 65 |
| SD | 20.3 | 3.52 | 0.33 | 0.20 | 0.32 | 19.89 | 100.3 | 12.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-M:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 321 | 44 | 11.7 | 7.4 | 3.5 | 3.9 | 17.7 | 259 | 74 |
| 322 | 48 | 17.4 | 7.9 | 3.8 | 4.1 | 20.4 | 546 | 70 |
| 323 | 63 | 1.2 | 7.5 | 4.2 | 3.3 | 59.2 | 272 | 62 |
| 324 | 62 | 8.6 | 7.0 | 3.9 | 3.1 | 20.4 | 364 | 86 |
| 325 | 53 | 18.7 | 7.5 | 4.1 | 3.4 | 28.2 | 339 | 71 |
| 326 | 67 | 15.3 | 8.1 | 4.4 | 3.7 | 70.6 | 420 | 62 |
| 327 | 60 | 5.9 | 7.1 | 3.8 | 3.3 | 39.0 | 498 | 68 |
| 328 | 50 | 18.3 | 7.4 | 4.1 | 3.3 | 29.2 | 295 | 79 |
| 329 | 57 | 11.6 | 7.2 | 4.1 | 3.1 | 79.3 | 346 | 73 |
| 330 | -- | -- | -- | -- | -- | -- | -- | -- |
| MEAN | 56 | 12.1 | 7.5 | 4.0 | 3.5 | 40.4 | 371 | 72 |
| SD | 7.7 | 6.02 | 0.36 | 0.27 | 0.35 | 23.37 | 99.4 | 7.7 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

| Animal ID | ALT IU/L | SDH IU/L | TP g/dL | ALB g/dL | GLOB g/dL | TBA umol/L | ALKP IU/L | CHOL mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 341 | 60 | 6.1 | 7.8 | 4.2 | 3.6 | 30.6 | 431 | 69 |
| 342 | 46 | 13.2 | 7.6 | 3.9 | 3.7 | 31.2 | 450 | 71 |
| 343 | 59 | 11.3 | 7.7 | 3.9 | 3.8 | 20.2 | 411 | 57 |
| 344 | 40 | 13.8 | 6.9 | 3.8 | 3.1 | 68.0 | 265 | 66 |
| 345 | 50 | 12.2 | 7.3 | 3.9 | 3.4 | 18.2 | 247 | 58 |
| 346 | 71 | 12.3 | 7.6 | 4.2 | 3.4 | 28.2 | 389 | 63 |
| 347 | 54 | 15.0 | 7.9 | 4.1 | 3.8 | 19.9 | 365 | 74 |
| 348 | 67 | 9.5 | 7.3 | 4.0 | 3.3 | 18.9 | 534 | 73 |
| 349 | 61 | 7.2 | 7.3 | 3.7 | 3.6 | 31.3 | 307 | 62 |
| 350 | 67 | 3.7 | 8.1 | 4.6 | 3.5 | 17.4 | 470 | 78 |
| MEAN | 58 | 10.4 | 7.6 | 4.0 | 3.5 | 28.4 | 387 | 67 |
| SD | 9.9 | 3.69 | 0.35 | 0.26 | 0.23 | 15.07 | 92.1 | 7.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-M:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 361 | 55 | 6.9 | 7.8 | 4.1 | 3.7 | 36.2 | 397 | 78 |
| 362 | 51 | 14.3 | 7.5 | 4.3 | 3.2 | 36.9 | 301 | 76 |
| 363 | 61 | 8.5 | 8.2 | 4.6 | 3.6 | 22.9 | 367 | 83 |
| 364 | 47 | 14.7 | 7.7 | 3.9 | 3.8 | 11.3 | 315 | 82 |
| 365 | 59 | 13.2 | 6.6 | 3.9 | 2.7 | 20.0 | 425 | 75 |
| 366 | 68 | 14.2 | 7.6 | 4.2 | 3.4 | 76.1 | 407 | 72 |
| 367 | 48 | 1.1 | 7.4 | 3.7 | 3.7 | 23.6 | 336 | 69 |
| 368 | 108 | 4.5 | 7.3 | 3.9 | 3.4 | 24.5 | 408 | 65 |
| 369 | 46 | 7.5 | 7.0 | 4.0 | 3.0 | 18.4 | 280 | 86 |
| 370 | 81 | 13.7 | 7.2 | 3.7 | 3.5 | 33.3 | 451 | 63 |
| MEAN | 62 | 9.9 | 7.4 | 4.0 | 3.4 | 30.3 | 369 | 75 |
| SD | 19.3 | 4.82 | 0.44 | 0.28 | 0.35 | 18.03 | 57.9 | 7.7 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

| Animal ID | BUN mg/dL | CREAT mg/dL | NA mEq/L | K mEq/L | CL mEq/L | CA mg/dL | IP mg/dL | GLU mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 301 | 13.9 | 0.55 | 145 | 5.97 | 108 | 10.2 | 9.7 | 150 |
| 302 | 15.5 | 0.52 | 142 | 5.87 | 106 | 11.1 | 9.9 | 148 |
| 303 | 16.5 | 0.49 | 144 | 5.78 | 107 | 11.2 | 10.8 | 151 |
| 304 | 15.8 | 0.55 | 142 | 5.35 | 107 | 10.7 | 9.4 | 150 |
| 305 | 15.6 | 0.54 | 145 | 5.89 | 100 | 10.0 | 7.4 | 138 |
| 306 | 15.7 | 0.55 | 145 | 5.84 | 109 | 10.9 | 10.0 | 153 |
| 307 | 19.1 | 0.67 | 145 | 4.32 | 113 | 11.7 | 10.4 | 227 |
| 308 | 19.2 | 0.55 | 144 | 5.92 | 108 | 10.8 | 10.2 | 145 |
| 309 | 13.9 | 0.57 | 147 | 6.29 | 108 | 10.2 | 9.1 | 132 |
| 310 | 17.8 | 0.52 | 144 | 5.44 | 109 | 10.1 | 9.6 | 155 |
| MEAN | 16.3 | 0.55 | 144 | 5.67 | 108 | 10.7 | 9.7 | 155 |
| SD | 1.88 | 0.047 | 1.5 | 0.542 | 3.2 | 0.56 | 0.93 | 26.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-M:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 321 | 13.3 | 0.45 | 144 | 5.94 | 103 | 10.7 | 8.2 | 138 |
| 322 | 12.9 | 0.51 | 146 | 6.28 | 99 | 10.4 | 8.2 | 131 |
| 323 | 19.1 | 0.57 | 142 | 5.65 | 113 | 11.7 | 10.3 | 169 |
| 324 | 18.8 | 0.53 | 144 | 5.71 | 108 | 10.8 | 9.0 | 147 |
| 325 | 12.5 | 0.49 | 144 | 6.54 | 101 | 9.9 | 10.2 | 154 |
| 326 | 22.3 | 0.62 | 143 | 4.43 | 117 | 11.4 | 11.1 | 250 |
| 327 | 16.3 | 0.53 | 143 | 7.43 | 104 | 10.7 | 8.0 | 157 |
| 328 | 15.5 | 0.54 | 144 | 6.09 | 105 | 10.8 | 9.2 | 159 |
| 329 | 17.3 | 0.54 | 144 | 5.36 | 106 | 11.0 | 9.1 | 147 |
| 330 | -- | -- | -- | -- | -- | -- | -- | -- |
| MEAN | 16.4 | 0.53 | 144 | 5.94 | 106 | 10.8 | 9.3 | 161 |
| SD | 3.29 | 0.048 | 1.1 | 0.827 | 5.7 | 0.52 | 1.08 | 35.1 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

| Animal ID | BUN mg/dL | CREAT mg/dL | NA mEq/L | K mEq/L | CL mEq/L | CA mg/dL | IP mg/dL | GLU mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 341 | 17.0 | 0.67 | 144 | 4.73 | 110 | 11.7 | 11.4 | 246 |
| 342 | 15.3 | 0.55 | 143 | 5.84 | 104 | 10.4 | 9.9 | 147 |
| 343 | 13.8 | 0.54 | 145 | 6.10 | 102 | 10.6 | 8.5 | 124 |
| 344 | 13.8 | 0.48 | 143 | 6.11 | 99 | 10.8 | 8.9 | 137 |
| 345 | 17.6 | 0.46 | 145 | 5.71 | 106 | 10.3 | 9.6 | 155 |
| 346 | 16.4 | 0.57 | 145 | 5.51 | 107 | 11.1 | 9.1 | 139 |
| 347 | 19.7 | 0.53 | 143 | 6.36 | 105 | 11.0 | 9.4 | 152 |
| 348 | 17.5 | 0.58 | 145 | 5.75 | 111 | 10.5 | 9.6 | 157 |
| 349 | 15.0 | 0.54 | 144 | 4.54 | 106 | 10.7 | 10.1 | 177 |
| 350 | 18.5 | 0.61 | 146 | 6.05 | 107 | 11.4 | 9.6 | 141 |
| MEAN | 16.5 | 0.55 | 144 | 5.67 | 106 | 10.9 | 9.6 | 158 |
| SD | 1.97 | 0.060 | 1.1 | 0.598 | 3.5 | 0.45 | 0.79 | 34.2 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-M:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 361 | 16.3 | 0.51 | 144 | 6.02 | 103 | 10.9 | 9.5 | 145 |
| 362 | 23.1 | 0.56 | 148 | 4.29 | 107 | 11.0 | 9.7 | 247 |
| 363 | 18.2 | 0.57 | 145 | 6.27 | 109 | 10.4 | 9.9 | 142 |
| 364 | 15.4 | 0.54 | 147 | 5.53 | 98 | 10.6 | 8.6 | 142 |
| 365 | 18.4 | 0.49 | 141 | 5.26 | 105 | 10.9 | 8.8 | 152 |
| 366 | 20.3 | 0.66 | 147 | 4.26 | 113 | 11.8 | 10.8 | 246 |
| 367 | 16.8 | 0.46 | 144 | 7.37 | 103 | 13.2 | 7.9 | 148 |
| 368 | 16.8 | 0.58 | 145 | 6.81 | 101 | 10.5 | 10.7 | 147 |
| 369 | 21.8 | 0.50 | 142 | 5.83 | 112 | 11.4 | 11.3 | 185 |
| 370 | 17.9 | 0.50 | 142 | 6.34 | 109 | 10.1 | 10.5 | 174 |
| MEAN | 18.5 | 0.54 | 145 | 5.80 | 106 | 11.1 | 9.8 | 173 |
| SD | 2.49 | 0.058 | 2.4 | 1.003 | 4.9 | 0.89 | 1.09 | 41.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0.- 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | ALT IU/L | SDH IU/L | TP g/dL | ALB g/dL | GLOB g/dL | TBA umol/L | ALKP IU/L | CHOL mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 311 | 51 | 8.4 | 7.6 | 4.0 | 3.6 | 14.9 | 231 | 71 |
| 312 | 47 | 14.9 | 8.0 | 4.4 | 3.6 | 15.0 | 281 | 60 |
| 313 | 54 | 15.9 | 6.9 | 3.7 | 3.2 | 17.4 | 191 | 62 |
| 314 | 64 | 11.9 | 8.5 | 4.7 | 3.8 | 37.0 | 258 | 75 |
| 315 | 54 | 12.6 | 7.8 | 4.3 | 3.5 | 24.3 | 194 | 72 |
| 316 | 63 | 17.8 | 7.4 | 4.0 | 3.4 | 52.3 | 229 | 60 |
| 317 | 62 | 12.2 | 7.8 | 4.0 | 3.8 | 21.2 | 247 | 60 |
| 318 | 54 | 12.9 | 7.2 | 3.9 | 3.3 | 37.5 | 246 | 60 |
| 319 | 52 | 9.4 | 6.9 | 4.5 | 2.4 | 20.6 | 251 | 79 |
| 320 | 76 | 9.8 | 8.0 | 4.1 | 3.9 | 14.8 | 207 | 60 |
| MEAN | 58 | 12.6 | 7.6 | 4.2 | 3.5 | 25.5 | 234 | 66 |
| SD | 8.5 | 2.98 | 0.52 | 0.31 | 0.43 | 12.65 | 29.1 | 7.5 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-F:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 331 | 52 | 15.9 | 8.2 | 4.5 | 3.7 | 23.9 | 185 | 57 |
| 332 | 32 | 12.3 | 9.0 | 4.0 | 5.0 | 18.6 | 19 | 61 |
| 333 | 42 | 10.2 | 7.1 | 4.0 | 3.1 | 10.0 | 160 | 56 |
| 334 | 48 | 20.3 | 7.6 | 4.2 | 3.4 | 19.6 | 242 | 57 |
| 335 | 52 | 15.0 | 7.6 | 4.3 | 3.3 | 24.9 | 406 | 58 |
| 336 | 55 | 10.4 | 7.7 | 4.6 | 3.1 | 19.8 | 335 | 68 |
| 337 | 48 | 18.6 | 8.5 | 4.7 | 3.8 | 17.9 | 277 | 80 |
| 338 | 60 | 5.3 | 7.8 | 4.5 | 3.3 | 21.5 | 319 | 48 |
| 339 | 63 | 12.9 | 7.8 | 4.5 | 3.3 | 20.1 | 260 | 72 |
| 340 | 53 | 12.6 | 7.7 | 4.3 | 3.4 | 14.1 | 181 | 65 |
| MEAN | 51 | 13.4 | 7.9 | 4.4 | 3.5 | 19.0 | 238 | 62 |
| SD | 8.8 | 4.35 | 0.54 | 0.24 | 0.56 | 4.39 | 108.7 | 9.2 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | ALT IU/L | SDH IU/L | TP g/dL | ALB g/dL | GLOB g/dL | TBA umol/L | ALKP IU/L | CHOL mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 351 | 52 | 13.9 | 8.0 | 4.7 | 3.3 | 19.4 | 261 | 66 |
| 352 | 51 | 20.5 | 7.5 | 4.2 | 3.3 | 12.5 | 357 | 59 |
| 353 | 65 | 16.7 | 9.1 | 5.2 | 3.9 | 13.1 | 193 | 81 |
| 354 | 47 | 13.9 | 7.9 | 4.7 | 3.2 | 15.3 | 161 | 53 |
| 355 | 56 | 13.4 | 8.2 | 4.7 | 3.5 | 19.3 | 130 | 62 |
| 356 | 56 | 18.6 | 7.7 | 4.5 | 3.2 | 18.1 | 368 | 69 |
| 357 | 47 | 10.4 | 8.4 | 4.7 | 3.7 | 17.8 | 257 | 69 |
| 358 | 90 | 21.0 | 7.5 | 4.2 | 3.3 | 18.0 | 217 | 59 |
| 359 | 64 | 20.3 | 7.8 | 4.4 | 3.4 | 18.8 | 229 | 54 |
| 360 | 54 | 17.4 | 8.0 | 4.6 | 3.4 | 14.6 | 217 | 71 |
| MEAN | 58 | 16.6 | 8.0 | 4.6 | 3.4 | 16.7 | 239 | 64 |
| SD | 12.7 | 3.59 | 0.48 | 0.29 | 0.23 | 2.59 | 76.4 | 8.6 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-F:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 371 | 51 | 4.3 | 8.7 | 4.7 | 4.0 | 24.5 | 181 | 89 |
| 372 | 49 | 14.7 | 7.3 | 4.1 | 3.2 | 19.2 | 325 | 57 |
| 373 | 100 | 13.7 | 8.2 | 4.8 | 3.4 | 23.8 | 242 | 75 |
| 374 | 48 | 8.7 | 8.4 | 4.5 | 3.9 | 19.3 | 298 | 88 |
| 375 | 63 | 11.3 | 7.4 | 4.0 | 3.4 | 27.2 | 286 | 73 |
| 376 | 45 | 0.1 | 7.3 | 4.2 | 3.1 | 19.4 | 409 | 63 |
| 377 | 43 | 10.6 | 7.7 | 4.3 | 3.4 | 21.7 | 289 | 69 |
| 378 | 50 | 10.0 | 8.6 | 4.4 | 4.2 | 13.5 | 369 | 77 |
| 379 | 46 | 11.1 | 8.3 | 4.5 | 3.8 | 17.3 | 305 | 77 |
| 380 | 61 | 14.0 | 7.3 | 4.1 | 3.2 | 27.7 | 189 | 56 |
| MEAN | 56 | 9.9 | 7.9 | 4.4 | 3.6 | 21.4 | 289 | 72 |
| SD | 16.9 | 4.56 | 0.58 | 0.27 | 0.38 | 4.49 | 71.7 | 11.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 -- 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | BUN mg/dL | CREAT mg/dL | NA mEq/L | K mEq/L | CL mEq/L | CA mg/dL | IP mg/dL | GLU mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 311 | 15.5 | 0.57 | 143 | 6.20 | 108 | 10.0 | 7.8 | 128 |
| 312 | 18.4 | 0.54 | 143 | 6.48 | 104 | 10.8 | 9.1 | 188 |
| 313 | 21.1 | 0.60 | 139 | 5.98 | 107 | 9.3 | 8.6 | 135 |
| 314 | 17.0 | 0.53 | 146 | 5.53 | 107 | 10.7 | 8.9 | 143 |
| 315 | 19.5 | 0.57 | 142 | 4.90 | 106 | 11.1 | 8.5 | 144 |
| 316 | 12.5 | 0.49 | 144 | 5.24 | 103 | 10.9 | 7.1 | 149 |
| 317 | 14.7 | 0.65 | 143 | 5.34 | 102 | 10.3 | 8.0 | 135 |
| 318 | 14.9 | 0.52 | 140 | 5.42 | 99 | 10.2 | 8.0 | 142 |
| 319 | 17.4 | 0.57 | 144 | 5.58 | 108 | 10.6 | 7.0 | 159 |
| 320 | 17.4 | 0.58 | 142 | 5.42 | 110 | 10.9 | 9.3 | 136 |
| MEAN | 16.8 | 0.56 | 143 | 5.61 | 105 | 10.5 | 8.2 | 146 |
| SD | 2.52 | 0.045 | 2.0 | 0.476 | 3.3 | 0.54 | 0.79 | 17.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-F:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 331 | 16.8 | 0.60 | 142 | 6.13 | 104 | 11.3 | 9.8 | 197 |
| 332 | 17.1 | 0.11 | 145 | 6.24 | 109 | 9.7 | 7.2 | 168 |
| 333 | 16.1 | 0.52 | 141 | 5.12 | 104 | 10.1 | 7.2 | 131 |
| 334 | 17.0 | 0.63 | 143 | 5.32 | 113 | 10.6 | 8.6 | 169 |
| 335 | 16.2 | 0.55 | 145 | 7.22 | 99 | 10.2 | 9.2 | 147 |
| 336 | 12.7 | 0.56 | 145 | 5.55 | 112 | 10.8 | 8.9 | 151 |
| 337 | 16.4 | 0.61 | 145 | 5.42 | 106 | 10.8 | 8.7 | 161 |
| 338 | 20.1 | 0.58 | 142 | 5.70 | 117 | 11.0 | 10.7 | 177 |
| 339 | 20.3 | 0.61 | 141 | 5.01 | 112 | 11.3 | 9.9 | 168 |
| 340 | 18.2 | 0.57 | 144 | 4.63 | 114 | 10.3 | 8.1 | 159 |
| MEAN | 17.1 | 0.53 | 143 | 5.63 | 109 | 10.6 | 8.8 | 163 |
| SD | 2.17 | 0.153 | 1.7 | 0.741 | 5.6 | 0.53 | 1.14 | 17.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | BUN mg/dL | CREAT mg/dL | NA mEq/L | K mEq/L | CL mEq/L | CA mg/dL | IP mg/dL | GLU mg/dL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 351 | 19.0 | 0.56 | 143 | 5.22 | 106 | 11.7 | 7.8 | 142 |
| 352 | 15.5 | 0.57 | 143 | 5.57 | 102 | 10.1 | 6.3 | 150 |
| 353 | 19.0 | 0.66 | 141 | 5.28 | 108 | 11.7 | 8.6 | 150 |
| 354 | 16.6 | 0.58 | 143 | 5.05 | 109 | 10.3 | 7.3 | 137 |
| 355 | 14.6 | 0.52 | 144 | 5.47 | 110 | 10.6 | 8.3 | 155 |
| 356 | 15.6 | 0.54 | 143 | 5.57 | 112 | 11.2 | 9.3 | 135 |
| 357 | 18.9 | 0.56 | 146 | 5.98 | 102 | 10.3 | 8.2 | 134 |
| 358 | 16.7 | 0.77 | 144 | 4.44 | 113 | 11.4 | 9.6 | 253 |
| 359 | 18.2 | 0.61 | 145 | 5.67 | 106 | 11.2 | 9.6 | 135 |
| 360 | 20.6 | 0.60 | 140 | 5.85 | 105 | 11.0 | 10.1 | 161 |
| MEAN | 17.5 | 0.60 | 143 | 5.41 | 107 | 11.0 | 8.5 | 155 |
| SD | 1.94 | 0.072 | 1.8 | 0.443 | 3.8 | 0.59 | 1.18 | 35.6 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-F:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 371 | 16.5 | 0.54 | 141 | 6.01 | 106 | 10.2 | 7.5 | 159 |
| 372 | 14.6 | 0.57 | 143 | 4.80 | 109 | 10.5 | 7.1 | 164 |
| 373 | 16.8 | 0.51 | 145 | 5.13 | 107 | 11.4 | 9.5 | 137 |
| 374 | 18.0 | 0.54 | 146 | 5.60 | 106 | 11.3 | 8.1 | 129 |
| 375 | 16.7 | 0.61 | 144 | 5.46 | 105 | 11.4 | 8.5 | 173 |
| 376 | 16.0 | 0.52 | 143 | 6.15 | 103 | 10.0 | 6.1 | 139 |
| 377 | 15.1 | 0.52 | 146 | 5.54 | 99 | 10.4 | 8.1 | 151 |
| 378 | 15.5 | 0.59 | 143 | 6.24 | 103 | 11.2 | 9.5 | 148 |
| 379 | 14.0 | 0.46 | 145 | 5.54 | 104 | 10.8 | 7.9 | 138 |
| 380 | 17.2 | 0.61 | 142 | 5.30 | 106 | 10.4 | 7.0 | 195 |
| MEAN | 16.0 | 0.55 | 144 | 5.58 | 105 | 10.8 | 7.9 | 153 |
| SD | 1.24 | 0.048 | 1.7 | 0.454 | 2.7 | 0.53 | 1.08 | 20.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 6

# INDIVIDUAL HEMATOLOGY DATA

## Hematology Test Directory

STUDY: UIC-12A

| NO. | ABBR. UNITS | DESCRIPTION PRECISION | CALCULATED | OPERAND A | OPERAND B | ---LOWER LIMIT--- MALE | FEMALE | ---UPPER LIMIT--- MALE | FEMALE |
|---|---|---|---|---|---|---|---|---|---|
| 1. | RBC<br>10^6/mm^3 | Erythrocytes<br>0.00 | NO | | | 6.50 | 6.50 | 9.00 | 9.00 |
| 2. | HGB<br>g/dL | Hemoglobin<br>0.0 | NO | | | 13.0 | 13.0 | 17.0 | 17.0 |
| 3. | HCT<br>% | Hematocrit<br>0.0 | NO | | | 40.0 | 40.0 | 50.0 | 50.0 |
| 4. | MCV<br>fL | Mean Corpuscular Volume<br>0.0 | NO | | | 50.0 | 50.0 | 65.0 | 65.0 |
| 5. | MCH<br>pg | Mean Corpuscular Hemoglobin<br>0.0 | NO | | | 18.0 | 18.0 | 23.0 | 23.0 |
| 6. | MCHC<br>g/dL | Mean Corpus. Hemo. Conc.<br>0.0 | NO | | | 32.0 | 32.0 | 39.0 | 39.0 |
| 7. | RETICS<br>% RBCs | Reticulocytes<br>0.0 | NO | | | 0.0 | 0.0 | 1.0 | 1.0 |
| 8. | PLT<br>10^3/mm^3 | Platelets<br>Integer | NO | | | 800 | 800 | 1400 | 1400 |
| 9. | WBC<br>10^3/mm^3 | Leukocytes<br>0.0 | NO | | | 9.0 | 6.0 | 18.0 | 15.0 |

(END OF REPORT)

08-JUN-1995

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

| Animal ID | RBC 10^6/mm^3 | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | RETICS % RBCs | PLT 10^3/mm^3 |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 301 | 7.52 | 15.5 | 42.2 | 56.1 | 20.6 | 36.7 | 0.1 | 952 |
| 302 | 7.76 | 16.2 | 43.2 | 55.7 | 20.9 | 37.5 | 0.2 | 1026 |
| 303 | 7.52 | 16.6 | 45.0 | 59.8 | 22.1 | 36.9 | 0.1 | 931 |
| 304 | 7.40 | 15.1 | 40.8 | 55.1 | 20.4 | 37.0 | 0.1 | 1293 |
| 305 | 8.04 | 16.4 | 45.1 | 56.1 | 20.4 | 36.4 | 0.1 | 985 |
| 306 | 7.41 | 16.0 | 43.9 | 59.2 | 21.6 | 36.4 | 0.1 | 848 |
| 307 | 7.42 | 15.9 | 43.4 | 58.5 | 21.4 | 36.6 | 0.0 | 911 |
| 308 | 7.80 | 16.1 | 44.3 | 56.8 | 20.6 | 36.3 | 0.3 | 837 |
| 309 | 7.78 | 15.4 | 42.1 | 54.1 | 19.8 | 36.6 | 0.0 | 870 |
| 310 | 7.33 | 14.9 | 40.9 | 55.8 | 20.3 | 36.4 | 0.0 | 1128 |
| MEAN | 7.60 | 15.8 | 43.1 | 56.7 | 20.8 | 36.7 | 0.1 | 978 |
| SD | 0.232 | 0.56 | 1.55 | 1.85 | 0.70 | 0.37 | 0.09 | 141.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-M:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 321 | 7.71 | 16.1 | 44.7 | 58.0 | 20.9 | 36.0 | 0.1 | 1033 |
| 322 | 7.54 | 16.2 | 44.4 | 58.9 | 21.5 | 36.5 | 0.2 | 991 |
| 323 | 7.47 | 15.3 | 41.8 | 56.0 | 20.5 | 36.6 | 0.3 | 828 |
| 324 | 7.57 | 15.5 | 42.9 | 56.7 | 20.5 | 36.1 | 0.0 | 1041 |
| 325 | 7.78 | 16.3 | 45.7 | 58.7 | 21.0 | 35.7 | 0.0 | 1011 |
| 326 | 8.26 | 16.0 | 43.8 | 53.0 | 19.4 | 36.5 | 0.0 | 1249 |
| 327 | 7.68 | 16.1 | 44.3 | 57.7 | 21.0 | 36.3 | 0.2 | 969 |
| 328 | 7.91 | 16.3 | 45.1 | 57.0 | 20.6 | 36.1 | 0.1 | 1086 |
| 329 | 7.65 | 14.9 | 41.4 | 54.1 | 19.5 | 36.0 | 0.4 | 1195 |
| 330 | -- | -- | -- | -- | -- | -- | -- | -- |
| MEAN | 7.73 | 15.9 | 43.8 | 56.7 | 20.5 | 36.2 | 0.1 | 1045 |
| SD | 0.238 | 0.50 | 1.47 | 2.02 | 0.69 | 0.30 | 0.14 | 123.9 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

| Animal ID | RBC 10^6/mm^3 | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | RETICS % RBCs | PLT 10^3/mm^3 |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 341 | 7.14 | 15.1 | 41.6 | 58.3 | 21.1 | 36.3 | 0.1 | 1083 |
| 342 | 7.95 | 16.2 | 46.5 | 58.5 | 20.4 | 34.8 | 0.3 | 880 |
| 343 | 7.95 | 16.4 | 44.7 | 56.2 | 20.6 | 36.7 | 0.1 | 983 |
| 344 | 7.61 | 15.9 | 44.0 | 57.8 | 20.9 | 36.1 | 0.0 | 1144 |
| 345 | 7.55 | 15.6 | 41.5 | 55.0 | 20.7 | 37.6 | 0.2 | 1027 |
| 346 | 8.41 | 16.3 | 45.7 | 54.3 | 19.4 | 35.7 | 0.0 | 904 |
| 347 | 7.44 | 15.9 | 46.3 | 62.2 | 21.4 | 34.3 | 0.1 | 1069 |
| 348 | 7.11 | 15.2 | 42.9 | 60.3 | 21.4 | 35.4 | 0.1 | 890 |
| 349 | 7.18 | 15.7 | 42.4 | 59.1 | 21.9 | 37.0 | 0.2 | 1026 |
| 350 | 7.36 | 16.0 | 43.1 | 58.6 | 21.7 | 37.1 | 0.0 | 1057 |
| MEAN | 7.57 | 15.8 | 43.9 | 58.0 | 21.0 | 36.1 | 0.1 | 1006 |
| SD | 0.422 | 0.44 | 1.87 | 2.38 | 0.73 | 1.06 | 0.10 | 89.8 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-M:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 361 | 7.45 | 16.0 | 43.9 | 58.9 | 21.5 | 36.4 | 0.0 | 1034 |
| 362 | 8.46 | 17.5 | 48.6 | 57.4 | 20.7 | 36.0 | 0.2 | 768 |
| 363 | 7.36 | 16.3 | 45.6 | 62.0 | 22.1 | 35.7 | 0.0 | 899 |
| 364 | 7.44 | 16.2 | 44.2 | 59.4 | 21.8 | 36.7 | 0.1 | 953 |
| 365 | 7.71 | 14.8 | 41.2 | 53.4 | 19.2 | 35.9 | 0.1 | 918 |
| 366 | 8.02 | 17.3 | 47.6 | 59.4 | 21.6 | 36.3 | 0.1 | 838 |
| 367 | 7.72 | 16.2 | 44.2 | 57.3 | 21.0 | 36.7 | 0.1 | 872 |
| 368 | 7.95 | 16.6 | 45.9 | 57.7 | 20.9 | 36.2 | 0.2 | 952 |
| 369 | 6.92 | 16.2 | 43.9 | 63.4 | 23.4 | 36.9 | 0.5 | 1092 |
| 370 | 7.72 | 16.3 | 44.4 | 57.5 | 21.1 | 36.7 | 0.3 | 897 |
| MEAN | 7.68 | 16.3 | 45.0 | 58.6 | 21.3 | 36.4 | 0.2 | 922 |
| SD | 0.420 | 0.74 | 2.09 | 2.75 | 1.08 | 0.40 | 0.15 | 92.9 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 1-M : VEHICLE (1.67 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 301 | Normal Red Blood Cells |
| 302 | Normal Red Blood Cells |
| 303 | Normal Red Blood Cells |
| 304 | Normal Red Blood Cells |
| 305 | Normal Red Blood Cells |
| 306 | Normal Red Blood Cells |
| 307 | Normal Red Blood Cells |
| 308 | Normal Red Blood Cells |
| 309 | Normal Red Blood Cells |
| 310 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 2-M : WR279396 (0.07 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 321 | Normal Red Blood Cells |
| 322 | Normal Red Blood Cells |
| 323 | Normal Red Blood Cells |
| 324 | Normal Red Blood Cells |
| 325 | Normal Red Blood Cells |
| 326 | Normal Red Blood Cells |
| 327 | Normal Red Blood Cells |
| 328 | Normal Red Blood Cells |
| 329 | Normal Red Blood Cells |
| 330 | -- |

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

GROUP: 3-M : WR279396 (0.33 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 341 | Normal Red Blood Cells |
| 342 | Normal Red Blood Cells |
| 343 | Normal Red Blood Cells |
| 344 | Normal Red Blood Cells |
| 345 | Normal Red Blood Cells |
| 346 | Normal Red Blood Cells |
| 347 | Normal Red Blood Cells |
| 348 | Normal Red Blood Cells |
| 349 | Normal Red Blood Cells |
| 350 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 4-M : WR279396 (1.67 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 361 | Normal Red Blood Cells |
| 362 | Normal Red Blood Cells |
| 363 | Normal Red Blood Cells |
| 364 | Normal Red Blood Cells |
| 365 | Normal Red Blood Cells |
| 366 | Normal Red Blood Cells |
| 367 | Normal Red Blood Cells |
| 368 | Normal Red Blood Cells |
| 369 | Normal Red Blood Cells |
| 370 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-M : VEHICLE (1.67 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 301 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 14.9 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.1 |
| 302 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.3 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 14.2 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.9 |
| 303 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 21 | 2.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 73 | 9.8 |
| | Monocytes | 6 | 0.8 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.4 |
| 304 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 5 | 1.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 93 | 18.6 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 20.0 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-M : VEHICLE (1.67 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 305 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 16.0 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.2 |
| 306 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.1 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 87 | 15.3 |
| | Monocytes | 4 | 0.7 |
| | Eosinophils | 2 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.6 |
| 307 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.0 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 92 | 15.3 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 16.6 |
| 308 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 25 | 5.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 72 | 14.3 |
| | Monocytes | 3 | 0.6 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 19.8 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176

GROUP: 1-M : VEHICLE (1.67 ml/kg/day)**

SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 309 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 12.1 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.8 |
| 310 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 2.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 18.4 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 2 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 21.2 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176

GROUP: 2-M : WR279396 (0.07 ml/kg/day)**

SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 321 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 16 | 3.5 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 81 | 17.5 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 21.6 |
| 322 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.6 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 16.9 |
| | Monocytes | 5 | 1.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 19.6 |
| 323 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 14 | 2.2 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 84 | 13.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.5 |
| 324 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 16 | 2.2 |
| | I. Neutrophils | 1 | 0.1 |
| | Lymphocytes | 79 | 11.1 |
| | Monocytes | 4 | 0.6 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.0 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUOY ID: UIC-12A
STUDY NO: 176 GROUP: 2-M : WR279396 (0.07 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 325 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 15 | 2.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 81 | 14.4 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.8 |
| 326 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 2 | 0.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 96 | 17.7 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.4 |
| 327 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 22 | 4.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 74 | 14.9 |
| | Monocytes | 4 | 0.8 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 20.2 |
| 328 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 90 | 16.9 |
| | Monocytes | 3 | 0.6 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.8 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-M : WR279396 (0.07 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 329 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 90 | 16.3 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.1 |
| 330 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 0 | -- |
| | I. Neutrophils | 0 | -- |
| | Lymphocytes | 0 | -- |
| | Monocytes | 0 | -- |
| | Eosinophils | 0 | -- |
| | Basophils | 0 | -- |
| | Atypical Lymphocytes | 0 | -- |
| | WBC | | -- |

WBC corrected for NRBC = or > 10 (--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 341 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 5 | 1.2 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 90 | 21.9 |
| | Monocytes | 3 | 0.7 |
| | Eosinophils | 2 | 0.5 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 24.3 |
| 342 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 15.2 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.1 |
| 343 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 15 | 3.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 82 | 16.6 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 2 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 20.2 |
| 344 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 14.8 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.2 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 345 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.3 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 10.2 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 11.7 |
| 346 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 14 | 2.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 84 | 12.7 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.1 |
| 347 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 7 | 1.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 93 | 22.5 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 24.2 |
| 348 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 21 | 3.1 |
| | I. Neutrophils | 2 | 0.3 |
| | Lymphocytes | 71 | 10.4 |
| | Monocytes | 5 | 0.7 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.7 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 349 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 12.2 |
| | Monocytes | 3 | 0.4 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.2 |
| 350 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 15.9 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 3 | 0.6 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.5 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 361 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.5 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 87 | 16.4 |
| | Monocytes | 3 | 0.6 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.8 |
| 362 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 93 | 14.8 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.9 |
| 363 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 90 | 16.0 |
| | Monocytes | 4 | 0.7 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.8 |
| 364 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 2.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 93 | 30.3 |
| | Monocytes | 1 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 32.6 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 365 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 15 | 2.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 81 | 11.0 |
| | Monocytes | 4 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.6 |
| 366 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 9 | 1.2 |
| | I. Neutrophils | 1 | 0.1 |
| | Lymphocytes | 88 | 12.1 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.7 |
| 367 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 33 | 6.8 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 63 | 13.0 |
| | Monocytes | 3 | 0.6 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 20.7 |
| 368 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 16.0 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 18.2 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 369 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 3 | 0.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 93 | 13.2 |
| | Monocytes | 4 | 0.6 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.2 |
| 370 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 5 | 1.2 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 94 | 23.4 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 24.9 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | RBC 10^6/mm^3 | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | RETICS % RBCs | PLT 10^3/mm^3 |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:VEHICLE (1.67 ml/kg/day)** | | | | | | | | |
| 311 | 6.70 | 14.7 | 39.2 | 58.5 | 21.9 | 37.5 | 0.2 | 1379 |
| 312 | 6.85 | 15.1 | 40.9 | 59.7 | 22.0 | 36.9 | 0.0 | 1182 |
| 313 | 6.94 | 14.9 | 39.5 | 56.9 | 21.5 | 37.7 | 0.1 | 1121 |
| 314 | 6.82 | 14.8 | 40.2 | 58.9 | 21.7 | 36.8 | 0.1 | 970 |
| 315 | 7.12 | 15.5 | 40.7 | 57.2 | 21.8 | 38.1 | 0.2 | 1161 |
| 316 | 7.36 | 15.7 | 42.5 | 57.7 | 21.3 | 36.9 | 0.3 | 978 |
| 317 | 7.35 | 16.1 | 42.9 | 58.4 | 21.9 | 37.5 | 0.0 | 1047 |
| 318 | 7.49 | 15.9 | 42.1 | 56.2 | 21.2 | 37.8 | 0.0 | 1160 |
| 319 | 7.69 | 15.9 | 44.8 | 58.3 | 20.7 | 35.5 | 0.4 | 1014 |
| 320 | 7.36 | 15.3 | 41.7 | 56.7 | 20.8 | 36.7 | 0.2 | 1134 |
| MEAN | 7.17 | 15.4 | 41.5 | 57.9 | 21.5 | 37.1 | 0.2 | 1115 |
| SD | 0.330 | 0.50 | 1.71 | 1.10 | 0.47 | 0.75 | 0.14 | 121.7 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 2-F:WR279396 (0.07 ml/kg/day)** | | | | | | | | |
| 331 | 7.02 | 15.8 | 42.2 | 60.1 | 22.5 | 37.4 | 0.2 | 1092 |
| 332 | 7.26 | 15.3 | 41.5 | 57.2 | 21.1 | 36.9 | 0.3 | 1274 |
| 333 | 7.08 | 15.2 | 39.7 | 56.1 | 21.5 | 38.3 | 0.2 | 1060 |
| 334 | 7.28 | 16.5 | 43.9 | 60.3 | 22.7 | 37.6 | 0.0 | 1090 |
| 335 | 7.44 | 16.0 | 42.6 | 57.3 | 21.5 | 37.6 | 0.2 | 931 |
| 336 | 7.02 | 15.5 | 40.8 | 58.1 | 22.1 | 38.0 | 0.1 | 1107 |
| 337 | 6.69 | 14.8 | 40.5 | 60.5 | 22.1 | 36.5 | 0.0 | 1100 |
| 338 | 6.55 | 14.4 | 38.6 | 58.9 | 22.0 | 37.3 | 0.3 | 752 |
| 339 | 7.13 | 15.0 | 40.2 | 56.4 | 21.0 | 37.3 | 0.8 | 931 |
| 340 | 8.22 | 18.1 | 47.6 | 57.9 | 22.0 | 38.0 | 0.0 | 838 |
| MEAN | 7.17 | 15.7 | 41.8 | 58.3 | 21.9 | 37.5 | 0.2 | 1018 |
| SD | 0.455 | 1.05 | 2.56 | 1.61 | 0.56 | 0.54 | 0.24 | 153.1 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
## PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

| Animal ID | RBC 10^6/mm^3 | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | RETICS % RBCs | PLT 10^3/mm^3 |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:WR279396 (0.33 ml/kg/day)** | | | | | | | | |
| 351 | 7.21 | 15.7 | 43.1 | 59.8 | 21.8 | 36.4 | 0.2 | 914 |
| 352 | 7.18 | 15.5 | 41.5 | 57.8 | 21.6 | 37.3 | 0.4 | 863 |
| 353 | 7.57 | 16.2 | 43.5 | 57.5 | 21.4 | 37.2 | 0.2 | 885 |
| 354 | 7.32 | 15.5 | 41.1 | 56.1 | 21.2 | 37.7 | 0.3 | 830 |
| 355 | 7.35 | 14.9 | 40.5 | 55.1 | 20.3 | 36.8 | 0.3 | 898 |
| 356 | 7.19 | 16.3 | 42.3 | 58.8 | 22.7 | 38.5 | 0.1 | 1120 |
| 357 | 7.09 | 15.1 | 41.2 | 58.1 | 21.3 | 36.7 | 0.2 | 1210 |
| 358 | 7.16 | 16.0 | 41.4 | 57.8 | 22.3 | 38.6 | 0.2 | 1111 |
| 359 | 7.41 | 15.7 | 42.4 | 57.2 | 21.2 | 37.0 | 0.0 | 1064 |
| 360 | 6.69 | 14.8 | 39.0 | 58.3 | 22.1 | 37.9 | 0.1 | 967 |
| MEAN | 7.22 | 15.6 | 41.6 | 57.7 | 21.6 | 37.4 | 0.2 | 986 |
| SD | 0.233 | 0.52 | 1.31 | 1.32 | 0.68 | 0.75 | 0.12 | 130.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GROUP: 4-F:WR279396 (1.67 ml/kg/day)** | | | | | | | | |
| 371 | 7.89 | 16.4 | 43.6 | 55.3 | 20.8 | 37.6 | 0.3 | 1300 |
| 372 | 6.62 | 14.5 | 37.9 | 57.3 | 21.9 | 38.3 | 0.0 | 1112 |
| 373 | 6.76 | 14.3 | 38.1 | 56.4 | 21.2 | 37.5 | 0.1 | 1111 |
| 374 | 7.21 | 15.2 | 41.2 | 57.1 | 21.1 | 36.9 | 0.0 | 1109 |
| 375 | 7.77 | 16.5 | 45.3 | 58.3 | 21.2 | 36.4 | 0.4 | 1120 |
| 376 | 7.12 | 15.1 | 40.6 | 57.0 | 21.2 | 37.2 | 0.1 | 1090 |
| 377 | 6.88 | 15.5 | 40.2 | 58.4 | 22.5 | 38.6 | 0.0 | 1082 |
| 378 | 7.68 | 15.9 | 43.5 | 56.6 | 20.7 | 36.6 | 0.2 | 1100 |
| 379 | 7.00 | 15.1 | 41.2 | 58.9 | 21.6 | 36.7 | 0.3 | 904 |
| 380 | 8.18 | 16.8 | 45.9 | 56.1 | 20.5 | 36.6 | 0.2 | 1080 |
| MEAN | 7.31 | 15.5 | 41.8 | 57.1 | 21.3 | 37.2 | 0.2 | 1101 |
| SD | 0.532 | 0.85 | 2.76 | 1.12 | 0.60 | 0.75 | 0.14 | 94.3 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 1-F : VEHICLE (1.67 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 311 | Normal Red Blood Cells |
| 312 | Normal Red Blood Cells |
| 313 | Normal Red Blood Cells |
| 314 | Normal Red Blood Cells |
| 315 | Normal Red Blood Cells |
| 316 | Normal Red Blood Cells |
| 317 | Normal Red Blood Cells |
| 318 | Normal Red Blood Cells |
| 319 | Normal Red Blood Cells |
| 320 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
GROUP: 2-F : WR279396 (0.07 ml/kg/day)**
SEX: FEMALE

| Animal ID | DAY27/28 |
|---|---|
| 331 | Normal Red Blood Cells |
| 332 | Normal Red Blood Cells |
| 333 | Normal Red Blood Cells |
| 334 | Normal Red Blood Cells |
| 335 | Normal Red Blood Cells |
| 336 | Normal Red Blood Cells |
| 337 | Normal Red Blood Cells |
| 338 | Normal Red Blood Cells |
| 339 | Normal Red Blood Cells |
| 340 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 3-F : WR279396 (0.33 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 351 | Normal Red Blood Cells |
| 352 | Normal Red Blood Cells |
| 353 | Normal Red Blood Cells |
| 354 | Normal Red Blood Cells |
| 355 | Normal Red Blood Cells |
| 356 | Normal Red Blood Cells |
| 357 | Normal Red Blood Cells |
| 358 | Normal Red Blood Cells |
| 359 | Normal Red Blood Cells |
| 360 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 4-F : WR279396 (1.67 ml/kg/day)**

| Animal ID | DAY27/28 |
|---|---|
| 371 | Normal Red Blood Cells |
| 372 | Normal Red Blood Cells |
| 373 | Normal Red Blood Cells |
| 374 | Normal Red Blood Cells |
| 375 | Normal Red Blood Cells |
| 376 | Normal Red Blood Cells |
| 377 | Normal Red Blood Cells |
| 378 | Normal Red Blood Cells |
| 379 | Normal Red Blood Cells |
| 380 | Normal Red Blood Cells |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 311 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 13 | 2.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 85 | 13.5 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.9 |
| 312 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 4 | 0.7 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 92 | 15.5 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 16.9 |
| 313 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 25 | 3.6 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 71 | 10.3 |
| | Monocytes | 3 | 0.4 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.5 |
| 314 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 3 | 0.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 95 | 23.0 |
| | Monocytes | 2 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 24.2 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 315 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 19 | 4.1 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 77 | 16.8 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 3 | 0.7 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 21.8 |
| 316 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 91 | 19.3 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 21.2 |
| 317 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 15.3 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.8 |
| 318 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 9 | 1.5 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 14.5 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 16.3 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 319 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 15.0 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.2 |
| 320 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.5 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 13.1 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.9 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 331 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.6 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 12.7 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.4 |
| 332 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 5 | 0.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 95 | 17.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.9 |
| 333 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 1.2 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 92 | 18.2 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 19.8 |
| 334 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 25 | 3.8 |
| | I. Neutrophils | 2 | 0.3 |
| | Lymphocytes | 71 | 10.9 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.3 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 335 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 1.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 15.8 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.7 |
| 336 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 18 | 2.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 81 | 8.8 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 10.9 |
| 337 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 14 | 2.2 |
| | I. Neutrophils | 1 | 0.2 |
| | Lymphocytes | 79 | 12.2 |
| | Monocytes | 5 | 0.8 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.4 |
| 338 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 88 | 13.9 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.8 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 339 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 1.3 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 86 | 11.3 |
| | Monocytes | 3 | 0.4 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.1 |
| 340 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 0 | 0.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 97 | 10.3 |
| | Monocytes | 2 | 0.2 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 10.6 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 351 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 15 | 2.3 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 83 | 12.6 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.2 |
| 352 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 12 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 84 | 12.5 |
| | Monocytes | 4 | 0.6 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.9 |
| 353 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 6 | 0.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 92 | 13.2 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.4 |
| 354 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 4 | 0.6 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 94 | 13.1 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.9 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 355 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 0.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 91 | 9.0 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 9.9 |
| 356 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 3 | 0.5 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 94 | 16.6 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 17.7 |
| 357 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 10 | 2.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 90 | 17.6 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 19.5 |
| 358 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 7 | 1.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 13.3 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 3 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.9 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 359 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 12 | 1.9 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 13.5 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.5 |
| 360 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 15 | 2.3 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 83 | 12.6 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 15.2 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 371 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.8 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 85 | 13.6 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 2 | 0.3 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 16.0 |
| 372 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 0.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 8.2 |
| | Monocytes | 2 | 0.2 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 9.2 |
| 373 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 4 | 0.5 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 95 | 12.8 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 13.5 |
| 374 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 12 | 1.7 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 85 | 12.2 |
| | Monocytes | 3 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.4 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 375 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 12 | 2.0 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 87 | 14.4 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 16.5 |
| 376 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 3 | 0.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 96 | 13.6 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.2 |
| 377 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 2 | 0.2 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 95 | 11.2 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 2 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 11.8 |
| 378 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 8 | 2.4 |
| | I. Neutrophils | 1 | 0.3 |
| | Lymphocytes | 88 | 26.7 |
| | Monocytes | 3 | 0.9 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 30.3 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

| Animal ID | | DAY27/28 CNT | ABS |
|---|---|---|---|
| 379 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 11 | 1.6 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 89 | 12.8 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 14.4 |
| 380 | Nucleated Red Cells | 0 | |
| | M. Neutrophils | 2 | 0.4 |
| | I. Neutrophils | 0 | 0.0 |
| | Lymphocytes | 96 | 19.3 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Atypical Lymphocytes | 0 | 0.0 |
| | WBC | | 20.1 |

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 7

# OPHTHALMOLOGY REPORT

# ANIMAL EYE ASSOCIATES

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May 11, 1995

OPHTHALMIC REPORT

UIC/TRL Study No. 176

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

During Week -1 (February 21, 1995), a sufficient number of male and female CD® rats were given ophthalmic examinations by indirect ophthalmoscopy to result in forty rats/sex which were within normal limits.

During Week 4 (March 21, 1995), seventy-nine rats which were used in the above-referenced study were re-examined (one rat died on study). One mid dose male (animal no. 350) appeared to have a zone of retinal and choroidal atrophy of its left eye. The lesion is typical of trauma to the eye (the globe) and not a test article-related effect. All other rats appeared similar (no lesions) to their pretest examination on February 21, 1995.

Sincerely,

Samuel J. Vainisi, D.V.M.
Professor of Comparative
Ophthalmology, U. of IL. at Chicago

Diplomate, American College of
Veterinary Ophthalmologists

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

## Ophthalmic Examinations
## Males

| Treatment Group | Animal Number | Week -1 R.E. | Week -1 L.E. | Week 4 R.E. | Week 4 L.E. |
|---|---|---|---|---|---|
| Vehicle 1.67 ml/kg/day[a] | 301 | WNL | WNL | WNL | WNL |
| | 302 | WNL | WNL | WNL | WNL |
| | 303 | WNL | WNL | WNL | WNL |
| | 304 | WNL | WNL | WNL | WNL |
| | 305 | WNL | WNL | WNL | WNL |
| | 306 | WNL | WNL | WNL | WNL |
| | 307 | WNL | WNL | WNL | WNL |
| | 308 | WNL | WNL | WNL | WNL |
| | 309 | WNL | WNL | WNL | WNL |
| | 310 | WNL | WNL | WNL | WNL |
| WR279396 0.07 ml/kg/day[a] | 321 | WNL | WNL | WNL | WNL |
| | 322 | WNL | WNL | WNL | WNL |
| | 323 | WNL | WNL | WNL | WNL |
| | 324 | WNL | WNL | WNL | WNL |
| | 325 | WNL | WNL | WNL | WNL |
| | 326 | WNL | WNL | WNL | WNL |
| | 327 | WNL | WNL | WNL | WNL |
| | 328 | WNL | WNL | WNL | WNL |
| | 329 | WNL | WNL | WNL | WNL |
| | 330 | WNL | WNL | * | * |
| WR279396 0.33 ml/kg/day[a] | 341 | WNL | WNL | WNL | WNL |
| | 342 | WNL | WNL | WNL | WNL |
| | 343 | WNL | WNL | WNL | WNL |
| | 344 | WNL | WNL | WNL | WNL |
| | 345 | WNL | WNL | WNL | WNL |
| | 346 | WNL | WNL | WNL | WNL |
| | 347 | WNL | WNL | WNL | WNL |
| | 348 | WNL | WNL | WNL | WNL |
| | 349 | WNL | WNL | WNL | WNL |
| | 350 | WNL | WNL | WNL | ZRCA |
| WR279396 1.67 ml/kg/day[a] | 361 | WNL | WNL | WNL | WNL |
| | 362 | WNL | WNL | WNL | WNL |
| | 363 | WNL | WNL | WNL | WNL |
| | 364 | WNL | WNL | WNL | WNL |
| | 365 | WNL | WNL | WNL | WNL |
| | 366 | WNL | WNL | WNL | WNL |
| | 367 | WNL | WNL | WNL | WNL |
| | 368 | WNL | WNL | WNL | WNL |
| | 369 | WNL | WNL | WNL | WNL |
| | 370 | WNL | WNL | WNL | WNL |

[a]On days 0 - 5, animals were treated twice daily with the shown volume of test article or vehicle control article.

R.E. = Right Eye
L.E. = Left Eye
* = Animal Previously Died
WNL = Within Normal Limits
ZRCA = Zone of Retinal and Choroidal Atrophy

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

## Ophthalmic Examinations
## Females

| Treatment Group | Animal Number | Week -1 R.E. | Week -1 L.E. | Week 4 R.E. | Week 4 L.E. |
|---|---|---|---|---|---|
| Vehicle 1.67 ml/kg/day[a] | 311 | WNL | WNL | WNL | WNL |
| | 312 | WNL | WNL | WNL | WNL |
| | 313 | WNL | WNL | WNL | WNL |
| | 314 | WNL | WNL | WNL | WNL |
| | 315 | WNL | WNL | WNL | WNL |
| | 316 | WNL | WNL | WNL | WNL |
| | 317 | WNL | WNL | WNL | WNL |
| | 318 | WNL | WNL | WNL | WNL |
| | 319 | WNL | WNL | WNL | WNL |
| | 320 | WNL | WNL | WNL | WNL |
| WR279396 0.07 ml/kg/day[a] | 331 | WNL | WNL | WNL | WNL |
| | 332 | WNL | WNL | WNL | WNL |
| | 333 | WNL | WNL | WNL | WNL |
| | 334 | WNL | WNL | WNL | WNL |
| | 335 | WNL | WNL | WNL | WNL |
| | 336 | WNL | WNL | WNL | WNL |
| | 337 | WNL | WNL | WNL | WNL |
| | 338 | WNL | WNL | WNL | WNL |
| | 339 | WNL | WNL | WNL | WNL |
| | 340 | WNL | WNL | WNL | WNL |
| WR279396 0.33 ml/kg/day[a] | 351 | WNL | WNL | WNL | WNL |
| | 352 | WNL | WNL | WNL | WNL |
| | 353 | WNL | WNL | WNL | WNL |
| | 354 | WNL | WNL | WNL | WNL |
| | 355 | WNL | WNL | WNL | WNL |
| | 356 | WNL | WNL | WNL | WNL |
| | 357 | WNL | WNL | WNL | WNL |
| | 358 | WNL | WNL | WNL | WNL |
| | 359 | WNL | WNL | WNL | WNL |
| | 360 | WNL | WNL | WNL | WNL |
| WR279396 1.67 ml/kg/day[a] | 371 | WNL | WNL | WNL | WNL |
| | 372 | WNL | WNL | WNL | WNL |
| | 373 | WNL | WNL | WNL | WNL |
| | 374 | WNL | WNL | WNL | WNL |
| | 375 | WNL | WNL | WNL | WNL |
| | 376 | WNL | WNL | WNL | WNL |
| | 377 | WNL | WNL | WNL | WNL |
| | 378 | WNL | WNL | WNL | WNL |
| | 379 | WNL | WNL | WNL | WNL |
| | 380 | WNL | WNL | WNL | WNL |

[a]On days 0 - 5, animals were treated twice daily with the shown volume of test article or vehicle control article.

R.E. = Right Eye
L.E. = Left Eye
* = Animal Previously Died
WNL = Within Normal Limits
ZRCA = Zone of Retinal and Choroidal Atrophy

# APPENDIX 8

# INDIVIDUAL ORGAN WEIGHTS

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 1-M - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 407 | 432 | 419 | 422 | 407 | 470 | 461 | 415 | 390 |
| Adrenal Glands (G) | 0.075 | 0.133 | 0.064 | 0.063 | 0.128 | 0.087 | 0.096 | 0.084 | 0.093 |
| % BRAIN WEIGHT | 3.40 | 6.22 | 2.91 | 3.00 | 5.37 | 3.91 | 4.47 | 3.80 | 4.14 |
| Brain (G) | 2.205 | 2.138 | 2.200 | 2.103 | 2.382 | 2.224 | 2.147 | 2.209 | 2.249 |
| Heart (G) | 1.459 | 1.818 | 1.295 | 1.166 | 1.394 | 1.564 | 1.439 | 1.080 | 1.773 |
| % BRAIN WEIGHT | 66.17 | 85.03 | 58.86 | 55.44 | 58.52 | 70.32 | 67.02 | 48.89 | 78.84 |
| Kidneys (G) | 3.494 | 3.419 | 3.113 | 3.464 | 4.435 | 3.811 | 4.289 | 3.779 | 3.026 |
| % BRAIN WEIGHT | 158.46 | 159.92 | 141.50 | 164.72 | 186.19 | 171.36 | 199.77 | 171.07 | 134.55 |
| Liver (G) | 15.430 | 19.386 | 17.702 | 19.009 | 17.020 | 20.114 | 17.941 | 19.560 | 16.040 |
| % BRAIN WEIGHT | 699.77 | 906.74 | 804.64 | 903.90 | 714.53 | 904.41 | 835.63 | 885.47 | 713.21 |
| Lung/Bronchi (G) | 2.168 | 2.474 | 1.835 | 2.139 | 2.618 | 2.328 | 2.251 | 2.594 | 2.076 |
| % BRAIN WEIGHT | 98.32 | 115.72 | 83.41 | 101.71 | 109.91 | 104.68 | 104.84 | 117.43 | 92.31 |
| Spleen (G) | 0.704 | 0.915 | 0.726 | 0.655 | 0.811 | 0.852 | 0.690 | 0.782 | 0.751 |
| % BRAIN WEIGHT | 31.93 | 42.80 | 33.00 | 31.15 | 34.05 | 38.31 | 32.14 | 35.40 | 33.39 |
| Testes (G) | 3.260 | 3.291 | 3.153 | 3.289 | 3.280 | 2.965 | 3.450 | 3.401 | 3.159 |
| % BRAIN WEIGHT | 147.85 | 153.93 | 143.32 | 156.40 | 137.70 | 133.32 | 160.69 | 153.96 | 140.46 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 1-M - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 310 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 452 |
| Adrenal Glands (G) | 0.084 |
| % BRAIN WEIGHT | 3.68 |
| Brain (G) | 2.283 |
| Heart (G) | 1.319 |
| % BRAIN WEIGHT | 57.77 |
| Kidneys (G) | 4.175 |
| % BRAIN WEIGHT | 182.87 |
| Liver (G) | 15.959 |
| % BRAIN WEIGHT | 699.04 |
| Lung/Bronchi (G) | 2.037 |
| % BRAIN WEIGHT | 89.22 |
| Spleen (G) | 1.102 |
| % BRAIN WEIGHT | 48.27 |
| Testes (G) | 3.970 |
| % BRAIN WEIGHT | 173.89 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 2-M - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 321 | 322 | 323 | 324 | 325 | 326 | 327 | 328 | 329 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 425 | 421 | 431 | 474 | 405 | 457 | 405 | 420 | 421 |
| Adrenal Glands (G) | 0.065 | 0.107 | 0.082 | 0.095 | 0.069 | 0.072 | 0.068 | 0.079 | 0.063 |
| % BRAIN WEIGHT | 2.85 | 4.54 | 3.67 | 4.44 | 2.99 | 3.20 | 3.44 | 3.54 | 2.86 |
| Brain (G) | 2.280 | 2.359 | 2.235 | 2.142 | 2.309 | 2.252 | 1.974 | 2.233 | 2.203 |
| Heart (G) | 1.610 | 1.601 | 1.183 | 1.396 | 1.526 | 1.637 | 1.364 | 1.395 | 1.211 |
| % BRAIN WEIGHT | 70.61 | 67.87 | 52.93 | 65.17 | 66.09 | 72.69 | 69.10 | 62.47 | 54.97 |
| Kidneys (G) | 4.737 | 4.443 | 3.827 | 3.392 | 4.228 | 4.389 | 3.523 | 3.526 | 4.170 |
| % BRAIN WEIGHT | 207.76 | 188.34 | 171.23 | 158.36 | 183.11 | 194.89 | 178.47 | 157.90 | 189.29 |
| Liver (G) | 17.756 | 16.040 | 17.279 | 19.025 | 14.947 | 19.249 | 16.683 | 15.350 | 17.892 |
| % BRAIN WEIGHT | 778.77 | 679.95 | 773.11 | 888.19 | 647.34 | 854.75 | 845.14 | 687.42 | 812.17 |
| Lung/Bronchi (G) | 2.510 | 2.268 | 2.390 | 2.475 | 2.383 | 2.293 | 2.332 | 2.573 | 2.245 |
| % BRAIN WEIGHT | 110.09 | 96.14 | 106.94 | 115.55 | 103.20 | 101.82 | 118.14 | 115.23 | 101.91 |
| Spleen (G) | 0.840 | 0.845 | 0.886 | 1.006 | 1.056 | 0.756 | 0.705 | 0.729 | 0.903 |
| % BRAIN WEIGHT | 36.84 | 35.82 | 39.64 | 46.97 | 45.73 | 33.57 | 35.71 | 32.65 | 40.99 |
| Testes (G) | 3.326 | 3.170 | 3.564 | 3.510 | 3.332 | 3.085 | 3.543 | 3.270 | 2.975 |
| % BRAIN WEIGHT | 145.88 | 134.38 | 159.46 | 163.87 | 144.30 | 136.99 | 179.48 | 146.44 | 135.04 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 3-M - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 341 | 342 | 343 | 344 | 345 | 346 | 347 | 348 | 349 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 487 | 437 | 430 | 432 | 430 | 381 | 454 | 446 | 463 |
| Adrenal Glands (G) | 0.087 | 0.114 | 0.075 | 0.078 | 0.072 | 0.072 | 0.044 | 0.060 | 0.147 |
| % BRAIN WEIGHT | 3.86 | 4.77 | 3.27 | 3.33 | 3.33 | 3.64 | 2.05 | 2.59 | 6.56 |
| Brain (G) | 2.253 | 2.388 | 2.293 | 2.342 | 2.161 | 1.976 | 2.144 | 2.315 | 2.240 |
| Heart (G) | 1.706 | 1.885 | 1.485 | 1.606 | 1.400 | 1.007 | 1.744 | 1.650 | 1.860 |
| % BRAIN WEIGHT | 75.72 | 78.94 | 64.76 | 68.57 | 64.78 | 50.96 | 81.34 | 71.27 | 83.04 |
| Kidneys (G) | 3.913 | 3.795 | 4.148 | 3.754 | 4.582 | 3.789 | 4.019 | 3.184 | 4.876 |
| % BRAIN WEIGHT | 173.68 | 158.92 | 180.90 | 160.29 | 212.03 | 191.75 | 187.45 | 137.54 | 217.68 |
| Liver (G) | 20.568 | 18.451 | 14.842 | 18.990 | 20.486 | 16.651 | 18.269 | 16.045 | 19.888 |
| % BRAIN WEIGHT | 912.92 | 772.65 | 647.27 | 810.85 | 947.99 | 842.66 | 852.10 | 693.09 | 887.86 |
| Lung/Bronchi (G) | 2.725 | 3.420 | 2.448 | 2.755 | 2.204 | 2.075 | 2.883 | 2.426 | 2.569 |
| % BRAIN WEIGHT | 120.95 | 143.22 | 106.76 | 117.63 | 101.99 | 105.01 | 134.47 | 104.79 | 114.69 |
| Spleen (G) | 0.839 | 0.716 | 0.773 | 0.773 | 0.792 | 0.694 | 0.968 | 0.927 | 0.707 |
| % BRAIN WEIGHT | 37.24 | 29.98 | 33.71 | 33.01 | 36.65 | 35.12 | 45.15 | 40.04 | 31.56 |
| Testes (G) | 3.430 | 3.258 | 3.189 | 3.736 | 3.450 | 2.939 | 3.231 | 3.622 | 3.184 |
| % BRAIN WEIGHT | 152.24 | 136.43 | 139.08 | 159.52 | 159.65 | 148.73 | 150.70 | 156.46 | 142.14 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 3-M - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 350 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 489 |
| Adrenal Glands (G) | 0.059 |
| % BRAIN WEIGHT | 2.62 |
| Brain (G) | 2.256 |
| Heart (G) | 1.585 |
| % BRAIN WEIGHT | 70.26 |
| Kidneys (G) | 3.770 |
| % BRAIN WEIGHT | 167.11 |
| Liver (G) | 19.693 |
| % BRAIN WEIGHT | 872.92 |
| Lung/Bronchi (G) | 3.479 |
| % BRAIN WEIGHT | 154.21 |
| Spleen (G) | 0.975 |
| % BRAIN WEIGHT | 43.22 |
| Testes (G) | 3.180 |
| % BRAIN WEIGHT | 140.96 |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 4-M - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 411 | 449 | 444 | 460 | 417 | 404 | 434 | 383 | 504 |
| Adrenal Glands (G) | 0.103 | 0.083 | 0.091 | 0.092 | 0.110 | 0.087 | 0.072 | 0.053 | 0.089 |
| % BRAIN WEIGHT | 4.46 | 4.01 | 4.29 | 4.25 | 4.65 | 4.33 | 3.40 | 2.60 | 4.24 |
| Brain (G) | 2.307 | 2.068 | 2.119 | 2.167 | 2.364 | 2.010 | 2.119 | 2.035 | 2.097 |
| Heart (G) | 1.300 | 1.511 | 1.271 | 1.399 | 1.530 | 1.193 | 1.461 | 1.592 | 1.581 |
| % BRAIN WEIGHT | 56.35 | 73.07 | 59.98 | 64.56 | 64.72 | 59.35 | 68.95 | 78.23 | 75.39 |
| Kidneys (G) | 4.400 | 3.533 | 2.281 | 4.060 | 4.143 | 3.807 | 3.596 | 3.347 | 4.452 |
| % BRAIN WEIGHT | 190.72 | 170.84 | 107.65 | 187.36 | 175.25 | 189.40 | 169.70 | 164.47 | 212.30 |
| Liver (G) | 16.748 | 20.482 | 16.450 | 17.746 | 16.565 | 16.420 | 15.748 | 16.046 | 21.882 |
| % BRAIN WEIGHT | 725.96 | 990.43 | 776.31 | 818.92 | 700.72 | 816.92 | 743.18 | 788.50 | 1043.49 |
| Lung/Bronchi (G) | 2.568 | 2.513 | 2.678 | 2.328 | 1.914 | 2.245 | 2.236 | 2.380 | 1.840 |
| % BRAIN WEIGHT | 111.31 | 121.52 | 126.38 | 107.43 | 80.96 | 111.69 | 105.52 | 116.95 | 87.74 |
| Spleen (G) | 0.875 | 0.903 | 0.978 | 1.179 | 0.641 | 0.689 | 0.794 | 0.629 | 0.882 |
| % BRAIN WEIGHT | 37.93 | 43.67 | 46.15 | 54.41 | 27.12 | 34.28 | 37.47 | 30.91 | 42.06 |
| Testes (G) | 3.960 | 3.535 | 3.024 | 3.479 | 3.446 | 2.934 | 2.876 | 3.063 | 4.141 |
| % BRAIN WEIGHT | 171.65 | 170.94 | 142.71 | 160.54 | 145.77 | 145.97 | 135.72 | 150.52 | 197.47 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 4-M - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 370 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 451 |
| Adrenal Glands (G) | 0.070 |
| % BRAIN WEIGHT | 3.03 |
| Brain (G) | 2.314 |
| Heart (G) | 1.320 |
| % BRAIN WEIGHT | 57.04 |
| Kidneys (G) | 3.723 |
| % BRAIN WEIGHT | 160.89 |
| Liver (G) | 16.617 |
| % BRAIN WEIGHT | 718.11 |
| Lung/Bronchi (G) | 2.764 |
| % BRAIN WEIGHT | 119.45 |
| Spleen (G) | 1.145 |
| % BRAIN WEIGHT | 49.48 |
| Testes (G) | 3.470 |
| % BRAIN WEIGHT | 149.96 |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 1-F - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 290 | 276 | 293 | 271 | 286 | 270 | 253 | 271 | 274 |
| Adrenal Glands (G) | 0.073 | 0.106 | 0.078 | 0.086 | 0.088 | 0.142 | 0.095 | 0.088 | 0.042 |
| % BRAIN WEIGHT | 3.30 | 5.17 | 3.59 | 4.32 | 4.45 | 6.61 | 4.49 | 3.92 | 2.05 |
| Brain (G) | 2.211 | 2.049 | 2.175 | 1.989 | 1.977 | 2.148 | 2.118 | 2.244 | 2.050 |
| Heart (G) | 1.082 | 0.762 | 1.064 | 0.964 | 0.891 | 1.281 | 0.805 | 0.933 | 1.272 |
| % BRAIN WEIGHT | 48.94 | 37.19 | 48.92 | 48.47 | 45.07 | 59.64 | 38.01 | 41.58 | 62.05 |
| Kidneys (G) | 2.209 | 3.028 | 2.039 | 2.979 | 2.712 | 2.612 | 2.084 | 2.358 | 2.772 |
| % BRAIN WEIGHT | 99.91 | 147.78 | 93.75 | 149.77 | 137.18 | 121.60 | 98.39 | 105.08 | 135.22 |
| Liver (G) | 13.166 | 11.904 | 12.605 | 13.705 | 11.604 | 11.385 | 9.229 | 9.637 | 10.986 |
| % BRAIN WEIGHT | 595.48 | 580.97 | 579.54 | 689.04 | 586.95 | 530.03 | 435.74 | 429.46 | 535.90 |
| Lung/Bronchi (G) | 1.655 | 2.023 | 1.646 | 1.426 | 2.293 | 2.027 | 1.773 | 1.641 | 3.042 |
| % BRAIN WEIGHT | 74.85 | 98.73 | 75.68 | 71.69 | 115.98 | 94.37 | 83.71 | 73.13 | 148.39 |
| Ovaries (G) | 0.248 | 0.170 | 0.130 | 0.186 | 0.117 | 0.317 | 0.151 | -- | 0.055 |
| % BRAIN WEIGHT | 11.22 | 8.30 | 5.98 | 9.35 | 5.92 | 14.76 | 7.13 | -- | 2.68 |
| Spleen (G) | 0.669 | 1.026 | 0.670 | 0.756 | 0.789 | 0.686 | 0.503 | 0.663 | 0.614 |
| % BRAIN WEIGHT | 30.26 | 50.07 | 30.80 | 38.01 | 39.91 | 31.94 | 23.75 | 29.55 | 29.95 |

(--)-Data Unavailiable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 1-F - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 320 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 288 |
| Adrenal Glands (G) | 0.093 |
| % BRAIN WEIGHT | 4.40 |
| Brain (G) | 2.112 |
| Heart (G) | 1.054 |
| % BRAIN WEIGHT | 49.91 |
| Kidneys (G) | 2.605 |
| % BRAIN WEIGHT | 123.34 |
| Liver (G) | 11.606 |
| % BRAIN WEIGHT | 549.53 |
| Lung/Bronchi (G) | 1.965 |
| % BRAIN WEIGHT | 93.04 |
| Ovaries (G) | 0.254 |
| % BRAIN WEIGHT | 12.03 |
| Spleen (G) | 0.816 |
| % BRAIN WEIGHT | 38.64 |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 2-F - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 331 | 332 | 333 | 334 | 335 | 336 | 337 | 338 | 339 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 269 | 311 | 267 | 318 | 261 | 281 | 292 | 311 | 283 |
| Adrenal Glands (G) | 0.104 | 0.095 | 0.110 | 0.079 | 0.085 | 0.097 | 0.102 | 0.106 | 0.113 |
| % BRAIN WEIGHT | 5.30 | 4.45 | 5.41 | 3.81 | 4.40 | 4.59 | 4.76 | 4.67 | 5.33 |
| Brain (G) | 1.963 | 2.137 | 2.035 | 2.074 | 1.931 | 2.112 | 2.145 | 2.272 | 2.120 |
| Heart (G) | 0.905 | 1.088 | 1.144 | 1.115 | 0.785 | 1.152 | 1.412 | 1.077 | 1.225 |
| % BRAIN WEIGHT | 46.10 | 50.91 | 56.22 | 53.76 | 40.65 | 54.55 | 65.83 | 47.40 | 57.78 |
| Kidneys (G) | 2.792 | 3.127 | 2.803 | 3.546 | 2.847 | 2.675 | 2.265 | 2.603 | 2.466 |
| % BRAIN WEIGHT | 142.23 | 146.33 | 137.74 | 170.97 | 147.44 | 126.66 | 105.59 | 114.57 | 116.32 |
| Liver (G) | 11.024 | 13.014 | 11.873 | 14.667 | 11.259 | 12.202 | 11.423 | 11.120 | 11.419 |
| % BRAIN WEIGHT | 561.59 | 608.98 | 583.44 | 707.18 | 583.07 | 577.75 | 532.54 | 489.44 | 538.63 |
| Lung/Bronchi (G) | 1.662 | 1.647 | 1.911 | 2.355 | 1.540 | 2.050 | 2.142 | 1.822 | 1.998 |
| % BRAIN WEIGHT | 84.67 | 77.07 | 93.91 | 113.55 | 79.75 | 97.06 | 99.86 | 80.19 | 94.25 |
| Ovaries (G) | 0.071 | 0.227 | 0.373 | 0.168 | 0.139 | 0.129 | 0.244 | 0.207 | 0.195 |
| % BRAIN WEIGHT | 3.62 | 10.62 | 18.33 | 8.10 | 7.20 | 6.11 | 11.38 | 9.11 | 9.20 |
| Spleen (G) | 0.507 | 0.720 | 0.806 | 0.826 | 0.561 | 0.496 | 0.753 | 0.864 | 0.658 |
| % BRAIN WEIGHT | 25.83 | 33.69 | 39.61 | 39.83 | 29.05 | 23.48 | 35.10 | 38.03 | 31.04 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE

GROUP: 2-F - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 340 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 287 |
| Adrenal Glands (G) | 0.086 |
| % BRAIN WEIGHT | 4.26 |
| Brain (G) | 2.021 |
| Heart (G) | 0.969 |
| % BRAIN WEIGHT | 47.95 |
| Kidneys (G) | 2.620 |
| % BRAIN WEIGHT | 129.64 |
| Liver (G) | 12.000 |
| % BRAIN WEIGHT | 593.77 |
| Lung/Bronchi (G) | 1.449 |
| % BRAIN WEIGHT | 71.70 |
| Ovaries (G) | 0.187 |
| % BRAIN WEIGHT | 9.25 |
| Spleen (G) | 0.544 |
| % BRAIN WEIGHT | 26.92 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 3-F - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 351 | 352 | 353 | 354 | 355 | 356 | 357 | 358 | 359 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 261 | 286 | 288 | 228 | 249 | 263 | 267 | 323 | 258 |
| Adrenal Glands (G) | 0.117 | 0.124 | 0.109 | 0.103 | 0.064 | 0.102 | 0.088 | 0.075 | 0.154 |
| % BRAIN WEIGHT | 5.76 | 5.52 | 5.41 | 5.56 | 3.17 | 4.86 | 4.54 | 3.77 | 7.20 |
| Brain (G) | 2.032 | 2.248 | 2.016 | 1.851 | 2.019 | 2.098 | 1.939 | 1.988 | 2.138 |
| Heart (G) | 0.834 | 1.073 | 1.091 | 0.700 | 0.880 | 0.813 | 1.009 | 0.987 | 1.177 |
| % BRAIN WEIGHT | 41.04 | 47.73 | 54.12 | 37.82 | 43.59 | 38.75 | 52.04 | 49.65 | 55.05 |
| Kidneys (G) | 2.176 | 2.503 | 3.082 | 2.218 | 2.175 | 2.599 | 2.472 | 3.277 | 2.963 |
| % BRAIN WEIGHT | 107.09 | 111.34 | 152.88 | 119.83 | 107.73 | 123.88 | 127.49 | 164.84 | 138.59 |
| Liver (G) | 10.480 | 11.455 | 12.517 | 9.606 | 10.623 | 10.378 | 11.237 | 13.390 | 10.670 |
| % BRAIN WEIGHT | 515.75 | 509.56 | 620.88 | 518.96 | 526.15 | 494.66 | 579.53 | 673.54 | 499.06 |
| Lung/Bronchi (G) | 1.629 | 2.415 | 1.724 | 1.553 | 1.821 | 1.495 | 1.799 | 2.147 | 1.899 |
| % BRAIN WEIGHT | 80.17 | 107.43 | 85.52 | 83.90 | 90.19 | 71.26 | 92.78 | 108.00 | 88.82 |
| Ovaries (G) | 0.223 | 0.186 | 0.123 | 0.133 | 0.110 | 0.156 | 0.143 | 0.160 | 0.351 |
| % BRAIN WEIGHT | 10.97 | 8.27 | 6.10 | 7.19 | 5.45 | 7.44 | 7.37 | 8.05 | 16.42 |
| Spleen (G) | 0.650 | 0.717 | 0.616 | 0.591 | 0.485 | 0.548 | 0.684 | 0.701 | 0.656 |
| % BRAIN WEIGHT | 31.99 | 31.90 | 30.56 | 31.93 | 24.02 | 26.12 | 35.28 | 35.26 | 30.68 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE

GROUP: 3-F - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 360 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 310 |
| Adrenal Glands (G) | 0.082 |
| % BRAIN WEIGHT | 4.69 |
| Brain (G) | 1.749 |
| Heart (G) | 1.019 |
| % BRAIN WEIGHT | 58.26 |
| Kidneys (G) | 2.680 |
| % BRAIN WEIGHT | 153.23 |
| Liver (G) | 13.147 |
| % BRAIN WEIGHT | 751.69 |
| Lung/Bronchi (G) | 1.949 |
| % BRAIN WEIGHT | 111.44 |
| Ovaries (G) | 0.108 |
| % BRAIN WEIGHT | 6.17 |
| Spleen (G) | 0.671 |
| % BRAIN WEIGHT | 38.36 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 4-F - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 |
|---|---|---|---|---|---|---|---|---|---|
| BODY WEIGHT (G) | 284 | 286 | 305 | 271 | 305 | 277 | 321 | 268 | 252 |
| Adrenal Glands (G) | 0.081 | 0.088 | 0.094 | 0.089 | 0.071 | 0.135 | 0.120 | 0.099 | 0.076 |
| % BRAIN WEIGHT | 3.97 | 4.15 | 4.50 | 3.99 | 3.75 | 6.61 | 6.07 | 4.82 | 4.04 |
| Brain (G) | 2.040 | 2.123 | 2.090 | 2.228 | 1.894 | 2.043 | 1.976 | 2.052 | 1.880 |
| Heart (G) | 1.068 | 0.948 | 1.427 | 0.808 | 1.171 | 0.908 | 1.039 | 0.848 | 0.884 |
| % BRAIN WEIGHT | 52.35 | 44.65 | 68.28 | 36.27 | 61.83 | 44.44 | 52.58 | 41.33 | 47.02 |
| Kidneys (G) | 2.376 | 2.660 | 2.910 | 2.214 | 2.684 | 3.050 | 2.842 | 2.689 | 2.661 |
| % BRAIN WEIGHT | 116.47 | 125.29 | 139.23 | 99.37 | 141.71 | 149.29 | 143.83 | 131.04 | 141.54 |
| Liver (G) | 11.284 | 11.480 | 14.718 | 11.460 | 11.470 | 11.271 | 12.806 | 11.024 | 9.905 |
| % BRAIN WEIGHT | 553.14 | 540.74 | 704.21 | 514.36 | 605.60 | 551.69 | 648.08 | 537.23 | 526.86 |
| Lung/Bronchi (G) | 1.904 | 1.710 | 1.769 | 1.940 | 1.964 | 1.965 | 1.808 | 1.801 | 1.721 |
| % BRAIN WEIGHT | 93.33 | 80.55 | 84.64 | 87.07 | 103.70 | 96.18 | 91.50 | 87.77 | 91.54 |
| Ovaries (G) | 0.170 | 0.118 | 0.250 | 0.114 | 0.156 | 0.183 | 0.134 | 0.162 | 0.174 |
| % BRAIN WEIGHT | 8.33 | 5.56 | 11.96 | 5.12 | 8.24 | 8.96 | 6.78 | 7.89 | 9.26 |
| Spleen (G) | 0.701 | 0.530 | 0.737 | 0.579 | 0.523 | 0.874 | 0.554 | 0.843 | 0.515 |
| % BRAIN WEIGHT | 34.36 | 24.96 | 35.26 | 25.99 | 27.61 | 42.78 | 28.04 | 41.08 | 27.39 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 4-F - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

| | |
|---|---|
| ANIMAL ID: | 380 |
| BALANCE NO.: | |
| BODY WEIGHT (G) | 255 |
| Adrenal Glands (G) | 0.114 |
| % BRAIN WEIGHT | 5.39 |
| Brain (G) | 2.116 |
| Heart (G) | 1.092 |
| % BRAIN WEIGHT | 51.61 |
| Kidneys (G) | 2.666 |
| % BRAIN WEIGHT | 125.99 |
| Liver (G) | 10.363 |
| % BRAIN WEIGHT | 489.74 |
| Lung/Bronchi (G) | 2.205 |
| % BRAIN WEIGHT | 104.21 |
| Ovaries (G) | 0.170 |
| % BRAIN WEIGHT | 8.03 |
| Spleen (G) | 0.599 |
| % BRAIN WEIGHT | 28.31 |

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

# APPENDIX 9

# PATHOLOGY REPORT

AMENDED

# FINAL PATHOLOGY REPORT FOR FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS UIC/TRL STUDY NUMBER 176

PREPARED
BY
PATHOLOGY ASSOCIATES INTERNATIONAL
2201 WEST CAMPBELL PARK DRIVE, SUITE 327
CHICAGO, IL 60612

FOR
TOXICOLOGY RESEARCH LABORATORY (M/C 868)
DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF ILLINOIS AT CHICAGO
COLLEGE OF MEDICINE
1940 WEST TAYLOR STREET
CHICAGO, IL 60612-7353

SEPTEMBER 13, 1995

THIS PAGE REVISED

study no. 176

Robert S Morrissey 9/28/95
signature date

# FINAL REPORT AMENDMENT

STUDY NAME FOUR WEEK DERMAL TOXICITY STUDY OF WR279396 IN CD RATS

STUDY NUMBER UIC/TRL SN 176

DATE OF FINAL REPORT September 13, 1995

PART OF FINAL REPORT TO BE AMENDED (EXACT LOCATION)

1. Title in pages 1, 4, 9, 11-18, 20-27, 29-47, and 49-56.

2. Line 6 and 10 of first paragraph of experimental design and line 1 of third paragraph of experimental design on page 4. Lines 9 and 10 of second paragraph on page 6. Line 6 of third paragraph on page 6. Line 1 of table I on page 7. Line 1 of footnote c and line 1 of footnote ** on page 8.

REASON FOR THE AMENDMENT Sponsor request and protocol amendment.

AMENDMENT (Attach additional sheets as necessary)

1. Change title to "FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD RATS"

2. Change "control", "vehicle", "vehicle control", and/or "vehicle control article" to "placebo (vehicle)" on pages 4, 6, 7 and 8.

APPROVALS --

9/28/95
DATE

R S Morrissey
STUDY PATHOLOGIST

9-28-95
DATE

QUALITY ASSURANCE

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# SECTION I

# PATHOLOGY NARRATIVE

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signature date



FINAL PATHOLOGY REPORT

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

## INTRODUCTION

This pathology report, submitted by Pathology Associates International (PAI) to Toxicology Research Laboratory (TRL), University of Illinois at Chicago, represents the histopathology findings for the study designated as "Four Week Toxicity Study of WR279396 After Daily Dermal Application in CD® Rats", UIC/TRL Study Number 176.

## EXPERIMENTAL DESIGN AND METHODS

Three groups (Groups 2-4), each composed of 10 male and 10 female CD® (Virus Antibody Free) rats, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) was 0.07, 0.33, and 1.67 ml/kg in groups 2, 3, and 4, respectively. This corresponds to a dose of 20, 100, and 500 mg/kg/day of paromomycin + 0.7, 3.3, and 16.7 mg/kg/day of gentamicin, respectively. A placebo (vehicle) group (Group 1) of 10 male and 10 female CD® (Virus Antibody Free) rats received the test article vehicle (Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Beginning on Day 6 and for the remainder of the study, due to the appearance of moderate to severe erythema in mid and high dose animals, the volume (amount) of test article or placebo (vehicle) administered was reduced to one-half the initial dose levels. On these days, the volume (amount) was administered once daily in the morning instead of as a split dose twice daily. The total treatment period was 28/29 days starting with Day 0. (See Table I, Summary of Experimental Design).

With the exception of one accidental death (low dose male) on Day 23, all animals were sacrificed and necropsied in random order on Study Days 28 and 29. Animals were anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and then perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). All necropsies were performed according to TRL Standard Operating Procedures and were conducted by PAI personnel, except for the low dose male (number 330) which was necropsied on the day of death by an approved TRL technician. Tissues required by the protocol (see Table II, Protocol-Required Tissues) were examined and placed in 10% neutral buffered formalin. Specimens of exposure area skin were collected from the dorsal thoracic region (clipped) and specimens of non-exposure area skin were collected from the dorsal lumbar region (unclipped).

Tissues required for histopathologic evaluation in placebo (vehicle) (Group 1) and high dose (Group 4) groups were trimmed and processed, and slides were prepared in accordance with PAI Standard Operating Procedures. Heads were decalcified and two transverse sections of ear were trimmed to include outer and middle ear in one section and cochlea in the other. These tissues were evaluated by light microscopy and the results were tabulated. Some tissues are inherently difficult to obtain in sections because of their small size (e.g. parathyroid gland and mammary gland). Tissues were recorded as "unsuitable for complete evaluation" when they were missing in both the original section and in recut and retrim attempts to obtain them. Skin, exposure area, was identified as a target organ. Kidneys, ears, sciatic nerve, and exposure area skin were trimmed and

processed, slides were prepared, and the tissues were examined microscopically for animals in the low and mid dose groups. Also, all gross lesions were examined microscopically.

Treatment-related lesions are summarized in Table III, Summary of Treatment-Related Lesions. Microscopic findings for all groups are summarized in the Project Summary Tables (Section II). The mean group severity scores are found in the Severity Summary Tables (Section III). The mean group severity scores were determined by dividing the sum of all severity scores for a finding by the number of tissues examined. Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data Tables (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings (Section V). The codes used as entries in these tables are explained in the Report Codes Table.

## RESULTS AND DISCUSSION

The Results and Discussion section is divided into three parts: Necropsy Findings, Diagnostic Terms, and Histopathology Findings. The Necropsy Findings portion gives lesions seen at necropsy that were test article-related. The Diagnostic Terms portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section were not necessarily considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues.

### Necropsy Findings

Gross lesions were observed in thymus, mandibular lymph node, eye, adrenal gland, and salivary gland. Gross observations are listed in the Correlation of Gross and Microscopic (Micro) Findings report in Section V. Microscopic findings were correlated with gross lesions when possible. All gross lesions were interpreted as incidental findings.

### Diagnostic Terms

The morphologic characteristics of observations and lesions which require comment are presented in subsequent paragraphs to aid in the interpretation of the data.

Skin

Acanthosis was diagnosed when epidermis was focally thickened due to a thicker than normal stratum spinosum layer. Hyperkeratosis was represented by multiple layers of retained keratinized epithelial cells. Scab was diagnosed when a focal accumulation of degenerate inflammatory cells was present in the keratinized layer of epidermis.

Kidney

Mineralization occurred as small foci of deeply basophilic granular material in the lumen of renal tubules at the corticomedullary junction. Chronic inflammation in renal cortex was represented by small foci of mature lymphocytes in interstitium around glomeruli and/or renal tubules. Progressive nephropathy was diagnosed when eosinophilic casts were noted in the lumen of renal tubules and/or when basophilic regenerative epithelium was present.

The remainder of the diagnoses used in this study were considered to be self-explanatory and were not discussed in this section.

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Histopathology Findings:

Skin, exposure site

Local areas of acanthosis were observed in epidermis of skin from exposure area in 0 of 10, 0 of 10, 1 of 10, and 3 of 10 male rats in groups 1, 2, 3, and 4, respectively. In females, similar areas of acanthosis were observed in epidermis of skin from exposure area in 1 of 10, 0 of 10, 0 of 10, and 4 of 10 rats in groups 1, 2, 3, and 4, respectively. Acanthosis was interpreted as a possible response to local irritant effects of the test article.

Hyperkeratosis was observed more frequently in exposure area skin than in non-exposure area skin. In males, hyperkeratosis was present in exposure area skin in 8 of 10, 7 of 10, 8 of 10, and 9 of 10 animals in groups 1, 2, 3, and 4, respectively, while the incidence was 0 of 10 and 2 of 10 in non-exposure area skin for groups 1 and 4, respectively. In females, hyperkeratosis was present in exposure area skin in 8 of 10, 3 of 10, 4 of 10, and 8 of 10 animals in groups 1, 2, 3, and 4, respectively, while the incidence was 1 of 10 and 0 of 10 in non-exposure area skin for groups 1 and 4, respectively. However, the combined administration of paromomycin and gentamicin did not affect the incidence of hyperkeratosis in exposure area skin in either male (8 of 10 vs. 9 of 10 in placebo (vehicle) and high dose males) or female (8 of 10 vs. 8 of 10 in placebo (vehicle) and high dose females) rats. Increased hyperkeratosis in exposure area skin was interpreted as a response to the vehicle and/or a response to rubbing during the application and/or removal of material.

Kidney

The incidence of chronic inflammation in the renal cortex of male rats was 2 of 10, 2 of 10, 3 of 10, and 3 of 10 for groups 1, 2, 3, and 4, respectively. In females, the incidence of chronic inflammation in the renal cortex was 3 of 10, 3 of 10, 2 of 10, and 6 of 10 in groups 1, 2, 3, and 4, respectively. The severity was minimal in all cases, and the change is a relatively common incidental finding. Therefore, I do not consider the slight difference between high dose and placebo (vehicle) females to be biologically significant. Also, the incidence of chronic inflammation in the renal cortex of males was similar in all groups, which further supports the position that the slight increase in incidence in high dose females was not a test article-related effect.

Kidney, exposure area skin, sciatic nerve, and ear were evaluated histopathologically for animal number 330 (low dose male), which was the only early death animal in the study. There was no indication of test article-related toxicity in the tissues evaluated.

## CONCLUSIONS

Under the conditions of this study, the daily dermal application of 1.67 ml/kg (1.67 ml/kg x 2 on Days 0-5) of WR279396 to rats for 28/29 days was associated with minimal or mild dermal acanthosis. Daily dermal application of lower volumes of WR279396, 0.33 or 0.07 ml/kg (0.33 or 0.07 ml/kg x 2 on Days 0-5), was not associated with any histologic changes.

Robert L Morrissey
Robert L. Morrissey, DVM, Ph.D.
Diplomate, ACVP

9/28/95
Date

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TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

| Treatment Group | Treatment | Paromomycin Dose Level (mg/kg/day) | Gentamicin Dose Level (mg/kg/day) | Dosing Volume (ml/kg/day) | Number of Males | Number of Females |
|---|---|---|---|---|---|---|
| 1 | Placebo (Vehicle) | 0 | 0 | 1.67 x 2 (1.67) | 10 | 10 |
| 2 | WR279396 | 20 (10) | 0.7 (0.04) | 0.07 x 2 (0.07) | 10 | 10 |
| 3 | WR279396 | 100 (50) | 3.3 (1.7) | 0.33 x 2 (0.33) | 10 | 10 |
| 4 | WR279396 | 500 (250) | 16.7 (8.4) | 1.67 x 2 (1.67) | 10 | 10 |

*Numbers in parentheses are dosages for Days 6 through 29.

TABLE II

PROTOCOL-REQUIRED TISSUES

Adrenal glands
Aorta
Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Heart
Ileum
Jejunum
Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
Liver
Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
Ovaries
Pancreas
Pituitary gland
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic, and lumbar)
Spleen
Sternum with bone marrow
Stomach
Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina
Gross lesions

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AFTER DAILY DERMAL APPLICATION IN CD® RATS
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Report Codes Table

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A. Codes applying to organs

| | |
|---|---|
| N | Tissues within normal histological limits |
| A | Autolysis precluding adequate evaluation |
| O | Paired organ missing |
| U | Tissues unsuitable for complete evaluation |
| S | Tissues not applicable to animal |
| R | Recut |
| * | Tissues not required by protocol |

---

B. Codes applying to microscopic diagnoses

| | |
|---|---|
| 1 | minimal |
| 2 | mild |
| 3 | moderate |
| 4 | marked |
| ( ) | focal |
| [ ] | diffuse |
| < > | multifocal |
| P | Present |
| B | Neoplasm, benign |
| M | Neoplasm, malignant without metastasis |
| C | Neoplasm, malignant with metastasis |
| X | Metastatic site (+) |
| I | Bilateral |
| L | Unilateral |
| - | No data entered |

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# SECTION II

# PROJECT SUMMARY TABLE

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| BRAIN | # EX | 10 | | 0 | | 0 | | 10 | |
| Dilatation, ventricle | | 7 | 70.0 | 0 | 0.0 | 0 | 0.0 | 6 | 60.0 |
| PITUITARY GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Cyst, pars distalis | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| CERVICAL CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| Degeneration, neuron | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| THYMUS | # EX | 10 | | 0 | | 0 | | 10 | |
| Hemorrhage, multifocal | | 8 | 80.0 | 0 | 0.0 | 0 | 0.0 | 7 | 70.0 |
| SALIVARY GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| PANCREAS | # EX | 10 | | 0 | | 0 | | 10 | |
| Hyperplasia, islet cell | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| MID-THORACIC CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| ADRENAL GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Ectopic adrenal | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Hypertrophy, cortex, multifocal | | 4 | 40.0 | 0 | 0.0 | 0 | 0.0 | 5 | 50.0 |
| LUMBAR CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| THYROID GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| PARATHYROID GLAND | # EX | 9 | | 0 | | 0 | | 8 | |
| TRACHEA | # EX | 10 | | 0 | | 0 | | 10 | |
| ESOPHAGUS | # EX | 10 | | 0 | | 0 | | 10 | |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| HEART | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic, multifocal | | 7 | 70.0 | 0 | 0.0 | 0 | 0.0 | 6 | 60.0 |
| AORTA | # EX | 10 | | 0 | | 0 | | 10 | |
| DUODENUM | # EX | 10 | | 0 | | 0 | | 10 | |
| COLON | # EX | 10 | | 0 | | 0 | | 10 | |
| STOMACH | # EX | 10 | | 0 | | 0 | | 10 | |
| LIVER | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic, multifocal | | 8 | 80.0 | 0 | 0.0 | 0 | 0.0 | 8 | 80.0 |
| Hypertrophy, centrilobular | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| SPLEEN | # EX | 10 | | 0 | | 0 | | 10 | |
| JEJUNUM | # EX | 10 | | 0 | | 0 | | 10 | |
| LUNG | # EX | 10 | | 0 | | 0 | | 10 | |
| Mineralization, intrinsic artery | | 3 | 30.0 | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 |
| Inflammation, acute, peribronchial | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Inflammation, acute, perivascular | | 4 | 40.0 | 0 | 0.0 | 0 | 0.0 | 3 | 30.0 |
| Inflammation, chronic, interstitium | | 3 | 30.0 | 0 | 0.0 | 0 | 0.0 | 3 | 30.0 |
| KIDNEY | # EX | 10 | | 10 | | 10 | | 10 | |
| Dilatation, pelvis | | 1 | 10.0 | 1 | 10.0 | 2 | 20.0 | 0 | 0.0 |
| Cyst | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Inflammation, chronic, cortex | | 2 | 20.0 | 2 | 20.0 | 3 | 30.0 | 3 | 30.0 |
| Nephropathy, progressive | | 1 | 10.0 | 0 | 0.0 | 1 | 10.0 | 3 | 30.0 |
| Mineralization | | 0 | 0.0 | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 |
| URINARY BLADDER | # EX | 10 | | 0 | | 0 | | 10 | |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| PROSTATE | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| SKIN (EXPOSURE AREA) | # EX | 10 | | 10 | | 10 | | 10 | |
| Hyperkeratosis | | 8 | 80.0 | 7 | 70.0 | 8 | 80.0 | 9 | 90.0 |
| Acanthosis | | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 | 3 | 30.0 |
| Inflammation, chronic, subepidermal | | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 | 0 | 0.0 |
| Scab | | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 | 0 | 0.0 |
| SKIN (NON-EXPOSURE AREA) | # EX | 10 | | 0 | | 0 | | 10 | |
| Hyperkeratosis | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 |
| MAMMARY GLAND | # EX | 10 | | 0 | | 0 | | 9 | |
| ILEUM | # EX | 10 | | 0 | | 0 | | 10 | |
| CECUM | # EX | 10 | | 0 | | 0 | | 10 | |
| LYMPH NODE, MESENTERIC | # EX | 10 | | 0 | | 0 | | 10 | |
| Hemorrhage | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| SKELETAL MUSCLE | # EX | 10 | | 0 | | 0 | | 10 | |
| SCIATIC NERVE | # EX | 10 | | 10 | | 10 | | 10 | |
| RECTUM | # EX | 10 | | 0 | | 0 | | 10 | |
| TESTES | # EX | 10 | | 0 | | 0 | | 10 | |
| EPIDIDYMIS | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| SEMINAL VESICLE | # EX | 10 | | 0 | | 0 | | 10 | |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| EAR | # EX | 10 | | 10 | | 10 | | 10 | |
| FEMUR | # EX | 10 | | 0 | | 0 | | 10 | |
| STERNUM | # EX | 10 | | 0 | | 0 | | 10 | |
| BONE MARROW | # EX | 10 | | 0 | | 0 | | 10 | |
| EYE | # EX | 10 | | 1 | | 0 | | 10 | |
| Inflammation, subacute, periorbital | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 |
| Hemorrhage, periorbital | | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| LACRIMAL GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 |
| LYMPH NODE, MANDIBULAR | # EX | 1 | | 1 | | 1 | | 2 | |
| Hemorrhage | | 1 | 100.0 | 0 | 0.0 | 1 | 100.0 | 1 | 50.0 |
| Hyperplasia, lymphoid | | 0 | 0.0 | 1 | 100.0 | 1 | 100.0 | 1 | 50.0 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| BRAIN | # EX | 10 | | 0 | | 0 | | 10 | |
| Dilatation, ventricle | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 3 | 30.0 |
| PITUITARY GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| CERVICAL CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| THYMUS | # EX | 10 | | 0 | | 0 | | 10 | |
| Hemorrhage, multifocal | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 3 | 30.0 |
| SALIVARY GLAND | # EX | 10 | | 0 | | 1 | | 10 | |
| Inflammation, chronic | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| PANCREAS | # EX | 10 | | 0 | | 0 | | 10 | |
| Hyperplasia, islet cell | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Atrophy, acinar | | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| MID-THORACIC CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| Chromatolysis, neuron | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| ADRENAL GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Ectopic adrenal | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Hypertrophy, cortex, multifocal | | 5 | 50.0 | 0 | 0.0 | 0 | 0.0 | 4 | 40.0 |
| LUMBAR CORD | # EX | 10 | | 0 | | 0 | | 10 | |
| THYROID GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| PARATHYROID GLAND | # EX | 8 | | 0 | | 0 | | 8 | |
| TRACHEA | # EX | 10 | | 0 | | 0 | | 10 | |
| ESOPHAGUS | # EX | 10 | | 0 | | 0 | | 10 | |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| HEART | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic, multifocal | | 7 | 70.0 | 0 | 0.0 | 0 | 0.0 | 5 | 50.0 |
| AORTA | # EX | 10 | | 0 | | 0 | | 10 | |
| DUODENUM | # EX | 10 | | 0 | | 0 | | 10 | |
| COLON | # EX | 10 | | 0 | | 0 | | 10 | |
| STOMACH | # EX | 10 | | 0 | | 0 | | 10 | |
| LIVER | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic, multifocal | | 8 | 80.0 | 0 | 0.0 | 0 | 0.0 | 8 | 80.0 |
| SPLEEN | # EX | 10 | | 0 | | 0 | | 10 | |
| JEJUNUM | # EX | 10 | | 0 | | 0 | | 10 | |
| LUNG | # EX | 10 | | 0 | | 0 | | 10 | |
| Mineralization, intrinsic artery | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 2 | 20.0 |
| Inflammation, acute, perivascular | | 7 | 70.0 | 0 | 0.0 | 0 | 0.0 | 6 | 60.0 |
| Inflammation, chronic, interstitium | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| Inflammation, pyogranulomatous, focal | | 5 | 50.0 | 0 | 0.0 | 0 | 0.0 | 6 | 60.0 |
| Hemorrhage | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 4 | 40.0 |
| KIDNEY | # EX | 10 | | 10 | | 10 | | 10 | |
| Dilatation, pelvis | | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 | 0 | 0.0 |
| Cyst | | 0 | 0.0 | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 |
| Inflammation, chronic, cortex | | 3 | 30.0 | 3 | 30.0 | 2 | 20.0 | 6 | 60.0 |
| Nephropathy, progressive | | 3 | 30.0 | 1 | 10.0 | 2 | 20.0 | 3 | 30.0 |
| Mineralization | | 9 | 90.0 | 6 | 60.0 | 6 | 60.0 | 7 | 70.0 |
| URINARY BLADDER | # EX | 10 | | 0 | | 0 | | 10 | |

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY IO : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| SKIN (EXPOSURE AREA) | # EX | 10 | | 10 | | 10 | | 10 | |
| Hyperkeratosis | | 8 | 80.0 | 3 | 30.0 | 4 | 40.0 | 8 | 80.0 |
| Acanthosis | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 4 | 40.0 |
| SKIN (NON-EXPOSURE AREA) | # EX | 10 | | 0 | | 0 | | 10 | |
| Hyperkeratosis | | 1 | 10.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| MAMMARY GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| ILEUM | # EX | 10 | | 0 | | 0 | | 10 | |
| CECUM | # EX | 10 | | 0 | | 0 | | 10 | |
| LYMPH NODE, MESENTERIC | # EX | 10 | | 0 | | 0 | | 10 | |
| SKELETAL MUSCLE | # EX | 10 | | 0 | | 0 | | 10 | |
| SCIATIC NERVE | # EX | 10 | | 10 | | 10 | | 10 | |
| RECTUM | # EX | 10 | | 0 | | 0 | | 10 | |
| OVARY | # EX | 10 | | 0 | | 0 | | 10 | |
| UTERUS | # EX | 10 | | 0 | | 0 | | 10 | |
| Dilatation | | 5 | 50.0 | 0 | 0.0 | 0 | 0.0 | 1 | 10.0 |
| VAGINA | # EX | 10 | | 0 | | 0 | | 10 | |
| EAR | # EX | 10 | | 10 | | 10 | | 10 | |
| FEMUR | # EX | 10 | | 0 | | 0 | | 10 | |
| STERNUM | # EX | 10 | | 0 | | 0 | | 10 | |

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PATHOLOGY ASSOCIATES INTERNATIONAL
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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | % | # | % | # | % | # | % |
| BONE MARROW | # EX | 10 | | 0 | | 0 | | 10 | |
| EYE | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, subacute, periorbital | | 3 | 30.0 | 0 | 0.0 | 0 | 0.0 | 5 | 50.0 |
| LACRIMAL GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 2 | 20.0 | 0 | 0.0 | 0 | 0.0 | 3 | 30.0 |
| LYMPH NODE, MANDIBULAR | # EX | 2 | | 1 | | 1 | | 0 | |
| Hyperplasia, lymphoid | | 1 | 50.0 | 1 | 100.0 | 1 | 100.0 | 0 | 0.0 |
| Accumulation, plasma cell | | 1 | 50.0 | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 |

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# SECTION III

# SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| BRAIN | # EX | 10 | 0 | 0 | 10 |
| Dilatation, ventricle | | 7 1.00 | 0 0.00 | 0 0.00 | 6 0.70 |
| PITUITARY GLAND | # EX | 10 | 0 | 0 | 10 |
| Cyst, pars distalis | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.20 |
| CERVICAL CORD | # EX | 10 | 0 | 0 | 10 |
| Degeneration, neuron | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| THYMUS | # EX | 10 | 0 | 0 | 10 |
| Hemorrhage, multifocal | | 8 1.10 | 0 0.00 | 0 0.00 | 7 0.70 |
| SALIVARY GLAND | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| PANCREAS | # EX | 10 | 0 | 0 | 10 |
| Hyperplasia, islet cell | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| MID-THORACIC CORD | # EX | 10 | 0 | 0 | 10 |
| ADRENAL GLAND | # EX | 10 | 0 | 0 | 10 |
| Ectopic adrenal | | 2 0.20 | 0 0.00 | 0 0.00 | 0 0.00 |
| Hypertrophy, cortex, multifocal | | 4 0.40 | 0 0.00 | 0 0.00 | 5 0.50 |
| LUMBAR CORD | # EX | 10 | 0 | 0 | 10 |
| THYROID GLAND | # EX | 10 | 0 | 0 | 10 |
| PARATHYROID GLAND | # EX | 9 | 0 | 0 | 8 |
| TRACHEA | # EX | 10 | 0 | 0 | 10 |
| ESOPHAGUS | # EX | 10 | 0 | 0 | 10 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| HEART | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic, multifocal | | 7 0.90 | 0 0.00 | 0 0.00 | 6 0.80 |
| AORTA | # EX | 10 | 0 | 0 | 10 |
| DUODENUM | # EX | 10 | 0 | 0 | 10 |
| COLON | # EX | 10 | 0 | 0 | 10 |
| STOMACH | # EX | 10 | 0 | 0 | 10 |
| LIVER | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic, multifocal | | 8 0.80 | 0 0.00 | 0 0.00 | 8 0.80 |
| Hypertrophy, centrilobular | | 1 0.10 | 0 0.00 | 0 0.00 | 1 0.10 |
| SPLEEN | # EX | 10 | 0 | 0 | 10 |
| JEJUNUM | # EX | 10 | 0 | 0 | 10 |
| LUNG | # EX | 10 | 0 | 0 | 10 |
| Mineralization, intrinsic artery | | 3 0.30 | 0 0.00 | 0 0.00 | 2 0.20 |
| Inflammation, acute, peribronchial | | 1 0.20 | 0 0.00 | 0 0.00 | 0 0.00 |
| Inflammation, acute, perivascular | | 4 0.40 | 0 0.00 | 0 0.00 | 3 0.60 |
| Inflammation, chronic, interstitium | | 3 0.30 | 0 0.00 | 0 0.00 | 3 0.30 |
| KIDNEY | # EX | 10 | 10 | 10 | 10 |
| Dilatation, pelvis | | 1 0.10 | 1 0.20 | 2 0.30 | 0 0.00 |
| Cyst | | 1 0.20 | 0 0.00 | 0 0.00 | 0 0.00 |
| Inflammation, chronic, cortex | | 2 0.20 | 2 0.20 | 3 0.30 | 3 0.30 |
| Nephropathy, progressive | | 1 0.10 | 0 0.00 | 1 0.10 | 3 0.30 |
| Mineralization | | 0 0.00 | 1 0.10 | 0 0.00 | 0 0.00 |
| URINARY BLADDER | # EX | 10 | 0 | 0 | 10 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| PROSTATE | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| SKIN (EXPOSURE AREA) | # EX | 10 | 10 | 10 | 10 |
| Hyperkeratosis | | 8 1.00 | 7 0.70 | 8 0.80 | 9 1.20 |
| Acanthosis | | 0 0.00 | 0 0.00 | 1 0.10 | 3 0.30 |
| Inflammation, chronic, subepidermal | | 0 0.00 | 0 0.00 | 2 0.20 | 0 0.00 |
| Scab | | 0 0.00 | 0 0.00 | 1 0.10 | 0 0.00 |
| SKIN (NON-EXPOSURE AREA) | # EX | 10 | 0 | 0 | 10 |
| Hyperkeratosis | | 0 0.00 | 0 0.00 | 0 0.00 | 2 0.20 |
| MAMMARY GLAND | # EX | 10 | 0 | 0 | 9 |
| ILEUM | # EX | 10 | 0 | 0 | 10 |
| CECUM | # EX | 10 | 0 | 0 | 10 |
| LYMPH NODE, MESENTERIC | # EX | 10 | 0 | 0 | 10 |
| Hemorrhage | | 1 0.10 | 0 0.00 | 0 0.00 | 0 0.00 |
| SKELETAL MUSCLE | # EX | 10 | 0 | 0 | 10 |
| SCIATIC NERVE | # EX | 10 | 10 | 10 | 10 |
| RECTUM | # EX | 10 | 0 | 0 | 10 |
| TESTES | # EX | 10 | 0 | 0 | 10 |
| EPIDIDYMIS | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| SEMINAL VESICLE | # EX | 10 | 0 | 0 | 10 |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

| GROUP: | | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | | 10 | | 10 | | 10 | |
| | | # | SEV | # | SEV | # | SEV | # | SEV |
| EAR | # EX | 10 | | 10 | | 10 | | 10 | |
| FEMUR | # EX | 10 | | 0 | | 0 | | 10 | |
| STERNUM | # EX | 10 | | 0 | | 0 | | 10 | |
| BONE MARROW | # EX | 10 | | 0 | | 0 | | 10 | |
| EYE | # EX | 10 | | 1 | | 0 | | 10 | |
| Inflammation, subacute, periorbital | | 1 | 0.20 | 0 | 0.00 | 0 | 0.00 | 2 | 0.20 |
| Hemorrhage, periorbital | | 0 | 0.00 | 1 | 2.00 | 0 | 0.00 | 0 | 0.00 |
| LACRIMAL GLAND | # EX | 10 | | 0 | | 0 | | 10 | |
| Inflammation, chronic | | 2 | 0.20 | 0 | 0.00 | 0 | 0.00 | 2 | 0.20 |
| LYMPH NODE, MANDIBULAR | # EX | 1 | | 1 | | 1 | | 2 | |
| Hemorrhage | | 1 | 1.00 | 0 | 0.00 | 1 | 2.00 | 1 | 0.50 |
| Hyperplasia, lymphoid | | 0 | 0.00 | 1 | 3.00 | 1 | 1.00 | 1 | 1.00 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| BRAIN | # EX | 10 | 0 | 0 | 10 |
| Dilatation, ventricle | | 2 0.20 | 0 0.00 | 0 0.00 | 3 0.30 |
| PITUITARY GLAND | # EX | 10 | 0 | 0 | 10 |
| CERVICAL CORD | # EX | 10 | 0 | 0 | 10 |
| THYMUS | # EX | 10 | 0 | 0 | 10 |
| Hemorrhage, multifocal | | 1 0.10 | 0 0.00 | 0 0.00 | 3 0.30 |
| SALIVARY GLAND | # EX | 10 | 0 | 1 | 10 |
| Inflammation, chronic | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| PANCREAS | # EX | 10 | 0 | 0 | 10 |
| Hyperplasia, islet cell | | 1 0.10 | 0 0.00 | 0 0.00 | 0 0.00 |
| Atrophy, acinar | | 0 0.00 | 0 0.00 | 0 0.00 | 1 0.10 |
| MID-THORACIC CORD | # EX | 10 | 0 | 0 | 10 |
| Chromatolysis, neuron | | 1 0.10 | 0 0.00 | 0 0.00 | 0 0.00 |
| ADRENAL GLAND | # EX | 10 | 0 | 0 | 10 |
| Ectopic adrenal | | 2 0.20 | 0 0.00 | 0 0.00 | 0 0.00 |
| Hypertrophy, cortex, multifocal | | 5 0.50 | 0 0.00 | 0 0.00 | 4 0.40 |
| LUMBAR CORD | # EX | 10 | 0 | 0 | 10 |
| THYROID GLAND | # EX | 10 | 0 | 0 | 10 |
| PARATHYROID GLAND | # EX | 8 | 0 | 0 | 8 |
| TRACHEA | # EX | 10 | 0 | 0 | 10 |
| ESOPHAGUS | # EX | 10 | 0 | 0 | 10 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| HEART | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic, multifocal | | 7 0.70 | 0 0.00 | 0 0.00 | 5 0.60 |
| AORTA | # EX | 10 | 0 | 0 | 10 |
| DUODENUM | # EX | 10 | 0 | 0 | 10 |
| COLON | # EX | 10 | 0 | 0 | 10 |
| STOMACH | # EX | 10 | 0 | 0 | 10 |
| LIVER | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic, multifocal | | 8 0.80 | 0 0.00 | 0 0.00 | 8 0.80 |
| SPLEEN | # EX | 10 | 0 | 0 | 10 |
| JEJUNUM | # EX | 10 | 0 | 0 | 10 |
| LUNG | # EX | 10 | 0 | 0 | 10 |
| Mineralization, intrinsic artery | | 2 0.20 | 0 0.00 | 0 0.00 | 2 0.20 |
| Inflammation, acute, perivascular | | 7 0.90 | 0 0.00 | 0 0.00 | 6 0.60 |
| Inflammation, chronic, interstitium | | 1 0.10 | 0 0.00 | 0 0.00 | 1 0.10 |
| Inflammation, pyogranulomatous, focal | | 5 0.50 | 0 0.00 | 0 0.00 | 6 0.60 |
| Hemorrhage | | 2 0.20 | 0 0.00 | 0 0.00 | 4 0.40 |
| KIDNEY | # EX | 10 | 10 | 10 | 10 |
| Dilatation, pelvis | | 0 0.00 | 0 0.00 | 1 0.10 | 0 0.00 |
| Cyst | | 0 0.00 | 1 0.10 | 0 0.00 | 0 0.00 |
| Inflammation, chronic, cortex | | 3 0.30 | 3 0.30 | 2 0.20 | 6 0.60 |
| Nephropathy, progressive | | 3 0.30 | 1 0.10 | 2 0.20 | 3 0.30 |
| Mineralization | | 9 1.20 | 6 0.70 | 6 0.60 | 7 0.80 |
| URINARY BLADDER | # EX | 10 | 0 | 0 | 10 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| SKIN (EXPOSURE AREA) | # EX | 10 | 10 | 10 | 10 |
| Hyperkeratosis | | 8 0.80 | 3 0.30 | 4 0.40 | 8 0.80 |
| Acanthosis | | 1 0.10 | 0 0.00 | 0 0.00 | 4 0.50 |
| SKIN (NON-EXPOSURE AREA) | # EX | 10 | 0 | 0 | 10 |
| Hyperkeratosis | | 1 0.10 | 0 0.00 | 0 0.00 | 0 0.00 |
| MAMMARY GLAND | # EX | 10 | 0 | 0 | 10 |
| ILEUM | # EX | 10 | 0 | 0 | 10 |
| CECUM | # EX | 10 | 0 | 0 | 10 |
| LYMPH NODE, MESENTERIC | # EX | 10 | 0 | 0 | 10 |
| SKELETAL MUSCLE | # EX | 10 | 0 | 0 | 10 |
| SCIATIC NERVE | # EX | 10 | 10 | 10 | 10 |
| RECTUM | # EX | 10 | 0 | 0 | 10 |
| OVARY | # EX | 10 | 0 | 0 | 10 |
| UTERUS | # EX | 10 | 0 | 0 | 10 |
| Dilatation | | 5 1.00 | 0 0.00 | 0 0.00 | 1 0.20 |
| VAGINA | # EX | 10 | 0 | 0 | 10 |
| EAR | # EX | 10 | 10 | 10 | 10 |
| FEMUR | # EX | 10 | 0 | 0 | 10 |
| STERNUM | # EX | 10 | 0 | 0 | 10 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

| GROUP: | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 10 | 10 | 10 | 10 |
| | | # SEV | # SEV | # SEV | # SEV |
| BONE MARROW | # EX | 10 | 0 | 0 | 10 |
| EYE | # EX | 10 | 0 | 0 | 10 |
| Inflammation, subacute, periorbital | | 3 0.30 | 0 0.00 | 0 0.00 | 5 0.70 |
| LACRIMAL GLAND | # EX | 10 | 0 | 0 | 10 |
| Inflammation, chronic | | 2 0.20 | 0 0.00 | 0 0.00 | 3 0.30 |
| LYMPH NODE, MANDIBULAR | # EX | 2 | 1 | 1 | 0 |
| Hyperplasia, lymphoid | | 1 1.00 | 1 2.00 | 1 3.00 | 0 0.00 |
| Accumulation, plasma cell | | 1 1.00 | 0 0.00 | 1 2.00 | 0 0.00 |

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# SECTION IV

# TABULATED ANIMAL DATA

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

| ANIMAL ID: | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 | 310 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAIN | N | | N | N | | | | | | |
| Dilatation, ventricle | - | 3 | - | - | 1 | 1 | 1 | 1 | 2 | 1 |
| PITUITARY GLAND | N | N | N | N | N | N | N | N | N | N |
| CERVICAL CORD | N | N | N | N | N | N | N | N | N | N |
| THYMUS | | | | | | | N | | | N |
| Hemorrhage, multifocal | 2 | 1 | 1 | 1 | 1 | 2 | - | 2 | 1 | - |
| SALIVARY GLAND | N | N | N | N | N | N | N | N | N | N |
| PANCREAS | N | N | N | N | N | N | N | N | N | N |
| MID-THORACIC CORD | N | N | N | N | N | N | N | N | N | N |
| ADRENAL GLAND | N | | N | N | | | | N | | N |
| Ectopic adrenal | - | 1 | - | - | - | - | - | - | 1 | - |
| Hypertrophy, cortex, multifocal | - | 1 | - | - | 1 | 1 | 1 | - | - | - |
| LUMBAR CORD | N | N | N | N | N | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N | N | N | N | N | N |
| PARATHYROID GLAND | N | N | N | N | U | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| HEART | | N | | N | | | | | N | |
| Inflammation, chronic, multifocal | 1 | - | 1 | - | 1 | 1 | 3 | 1 | - | 1 |

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See Reports Code Table for Symbol Definitions

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

| ANIMAL ID: | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 | 310 |
|---|---|---|---|---|---|---|---|---|---|---|
| AORTA | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| COLON | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| LIVER | | | | | | | N | N | | |
| Inflammation, chronic, multifocal | 1 | 1 | 1 | 1 | 1 | 1 | - | - | 1 | 1 |
| Hypertrophy, centrilobular | - | - | - | 1 | - | - | - | - | - | - |
| SPLEEN | N | N | N | N | N | N | N | N | N | N |
| JEJUNUM | N | N | N | N | N | N | N | N | N | N |
| LUNG | N | | | N | | | | | N | |
| Mineralization, intrinsic artery | - | 1 | - | - | 1 | - | - | 1 | - | - |
| Inflammation, acute, peribronchial | - | - | 2 | - | - | - | - | - | - | - |
| Inflammation, acute, perivascular | - | - | 1 | - | 1 | 1 | 1 | - | - | - |
| Inflammation, chronic, interstitium | - | - | - | - | - | 1 | 1 | - | - | 1 |
| KIDNEY | N | N | N | N | N | N | | | | N |
| Dilatation, pelvis | - | - | - | - | - | - | 1 | - | - | - |
| Cyst | - | - | - | - | - | - | - | 2 | - | - |
| Inflammation, chronic, cortex | - | - | - | - | - | - | - | 1 | 1 | - |
| Nephropathy, progressive | - | - | - | - | - | - | - | 1 | - | - |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |
| PROSTATE | N | N | N | N | N | N | N | N | N | N |
| SKIN (EXPOSURE AREA) | N | | | | | | | | N | |
| Hyperkeratosis | - | 1 | 2 | 2 | 1 | 1 | 1 | 1 | - | 1 |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

| ANIMAL ID: | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 | 310 |
|---|---|---|---|---|---|---|---|---|---|---|
| SKIN (NON-EXPOSURE AREA) | N | N | N | N | N | N | N | N | N | N |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N |
| ILEUM | N | N | N | N | N | N | N | N | N | N |
| CECUM | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC | N | N | N | N | N | N | N | N | | N |
| Hemorrhage | - | - | - | - | - | - | - | - | 1 | - |
| SKELETAL MUSCLE | N | N | N | N | N | N | N | N | N | N |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| RECTUM | N | N | N | N | N | N | N | N | N | N |
| TESTES | N | N | N | N | N | N | N | N | N | N |
| EPIDIDYMIS | N | N | N | N | N | N | N | N | N | N |
| SEMINAL VESICLE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| FEMUR | N | N | N | N | N | N | N | N | N | N |
| STERNUM | N | N | N | N | N | N | N | N | N | N |
| BONE MARROW | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | | N | N | N |
| Inflammation, subacute, periorbital | - | - | - | - | - | - | 2 | - | - | - |
| LACRIMAL GLAND | N | N | | N | N | N | N | N | N | |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: MALE

| ANIMAL ID: | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 | 310 |
|---|---|---|---|---|---|---|---|---|---|---|
| LACRIMAL GLAND | N | N | | N | N | N | N | N | N | |
| Inflammation, chronic | - | - | 1 | - | - | - | - | - | - | 1 |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hemorrhage | - | - | - | - | - | - | 1 | - | - | - |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 2
SEX: MALE

| ANIMAL ID: | 321 | 322 | 323 | 324 | 325 | 326 | 327 | 328 | 329 | 330 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | | | | | N | N | N | N | N | N |
| Dilatation, pelvis | 2 | - | - | - | - | - | - | - | - | - |
| Inflammation, chronic, cortex | - | 1 | - | 1 | - | - | - | - | - | - |
| Mineralization | - | - | 1 | - | - | - | - | - | - | - |
| SKIN (EXPOSURE AREA) | | | | | | N | N | N | | |
| Hyperkeratosis | 1 | 1 | 1 | 1 | 1 | - | - | - | 1 | 1 |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| EYE | | | | | | | | | | |
| Hemorrhage, periorbital | - | - | - | - | - | 2 | - | - | - | - |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hyperplasia, lymphoid | 3 | - | - | - | - | - | - | - | - | - |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 3
SEX: MALE

| ANIMAL ID: | 341 | 342 | 343 | 344 | 345 | 346 | 347 | 348 | 349 | 350 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | N | N | | | | N | N | N | N | |
| Dilatation, pelvis | - | - | 1 | - | - | - | - | - | - | 2 |
| Inflammation, chronic, cortex | - | - | 1 | 1 | - | - | - | - | - | 1 |
| Nephropathy, progressive | - | - | - | - | 1 | - | - | - | - | - |
| SKIN (EXPOSURE AREA) | | | | | N | | | | | |
| Hyperkeratosis | 1 | 1 | 1 | 1 | - | 1 | - | 1 | 1 | 1 |
| Acanthosis | - | - | 1 | - | - | - | - | - | - | - |
| Inflammation, chronic, subepidermal | - | - | 1 | - | - | - | 1 | - | - | - |
| Scab | - | - | - | - | - | - | 1 | - | - | - |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hemorrhage | 2 | - | - | - | - | - | - | - | - | - |
| Hyperplasia, lymphoid | 1 | - | - | - | - | - | - | - | - | - |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

| ANIMAL ID: | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 | 370 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAIN | N | | | N | N | | | N | | |
| Dilatation, ventricle | - | 1 | 2 | - | - | 1 | 1 | - | 1 | 1 |
| PITUITARY GLAND | N | N | N | N | | N | N | N | N | N |
| Cyst, pars distalis | - | - | - | - | 2 | - | - | - | - | - |
| CERVICAL CORD | N | N | N | N | | N | N | N | N | N |
| Degeneration, neuron | - | - | - | - | 1 | - | - | - | - | - |
| THYMUS | | | | N | N | | | | | N |
| Hemorrhage, multifocal | 1 | 1 | 1 | - | - | 1 | 1 | 1 | 1 | - |
| SALIVARY GLAND | | N | N | N | N | N | N | N | N | N |
| Inflammation, chronic | 1 | - | - | - | - | - | - | - | - | - |
| PANCREAS | N | N | N | N | N | N | | N | N | N |
| Hyperplasia, islet cell | - | - | - | - | - | - | 1 | - | - | - |
| MID-THORACIC CORD | N | N | N | N | N | N | N | N | N | N |
| ADRENAL GLAND | N | | N | N | | | | | N | N |
| Hypertrophy, cortex, multifocal | - | 1 | - | - | 1 | 1 | 1 | 1 | - | - |
| LUMBAR CORD | N | N | N | N | N | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N | N | N | N | N | N |
| PARATHYROID GLAND | N | N | N | U | N | N | U | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| HEART | N | | | | N | | N | | N | |
| Inflammation, chronic, multifocal | - | 3 | 1 | 1 | - | 1 | - | 1 | - | 1 |

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## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 4
SEX: MALE

| ANIMAL ID: | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 | 370 |
|---|---|---|---|---|---|---|---|---|---|---|
| AORTA | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| COLON | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| LIVER | | N | | | N | | | | | |
| Inflammation, chronic, multifocal | 1 | - | 1 | 1 | - | 1 | 1 | 1 | 1 | 1 |
| Hypertrophy, centrilobular | - | - | - | - | - | - | - | 1 | - | - |
| SPLEEN | N | N | N | N | N | N | N | N | N | N |
| JEJUNUM | N | N | N | N | N | N | N | N | N | N |
| LUNG | | | | | N | N | | | | N |
| Mineralization, intrinsic artery | 1 | - | - | - | - | - | 1 | - | - | - |
| Inflammation, acute, perivascular | - | 2 | 2 | 2 | - | - | - | - | - | - |
| Inflammation, chronic, interstitium | - | - | 1 | - | - | - | - | 1 | 1 | - |
| KIDNEY | | N | N | | N | | N | N | | N |
| Inflammation, chronic, cortex | 1 | - | - | 1 | - | - | - | - | 1 | - |
| Nephropathy, progressive | 1 | - | - | - | - | 1 | - | - | 1 | - |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |
| PROSTATE | N | N | N | N | N | N | N | N | N | |
| Inflammation, chronic | - | - | - | - | - | - | - | - | - | 1 |
| SKIN (EXPOSURE AREA) | | | N | | | | | | | |
| Hyperkeratosis | 1 | 1 | - | 1 | 1 | 2 | 2 | 1 | 2 | 1 |
| Acanthosis | - | - | - | 1 | - | - | 1 | - | 1 | - |
| SKIN (NON-EXPOSURE AREA) | N | N | N | N | N | | | N | N | N |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

| ANIMAL ID: | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 | 370 |
|---|---|---|---|---|---|---|---|---|---|---|
| SKIN (NON-EXPOSURE AREA) | N | N | N | N | N | | | N | N | N |
| Hyperkeratosis | - | - | - | - | - | 1 | 1 | - | - | - |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | U | N |
| ILEUM | N | N | N | N | N | N | N | N | N | N |
| CECUM | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC | N | N | N | N | N | N | N | N | N | N |
| SKELETAL MUSCLE | N | N | N | N | N | N | N | N | N | N |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| RECTUM | N | N | N | N | N | N | N | N | N | N |
| TESTES | N | N | N | N | N | N | N | N | N | N |
| EPIDIDYMIS | N | N | N | | N | N | N | N | N | N |
| Inflammation, chronic | - | - | - | 1 | - | - | - | - | - | - |
| SEMINAL VESICLE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| FEMUR | N | N | N | N | N | N | N | N | N | N |
| STERNUM | N | N | N | N | N | N | N | N | N | N |
| BONE MARROW | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | | N | N | N | | N |
| Inflammation, subacute, periorbital | - | - | - | - | 1 | - | - | - | 1 | - |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

| ANIMAL ID: | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 | 370 |
|---|---|---|---|---|---|---|---|---|---|---|
| LACRIMAL GLAND | N | N | N | | N | N | N | N | N | |
| Inflammation, chronic | - | - | - | 1 | - | - | - | - | - | 1 |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hemorrhage | - | 1 | - | - | - | - | - | - | - | - |
| Hyperplasia, lymphoid | - | - | - | - | - | - | 2 | - | - | - |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: FEMALE

| ANIMAL ID: | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAIN | N | N | N | N | N | N | | N | N | |
| Dilatation, ventricle | - | - | - | - | - | - | 1 | - | - | 1 |
| PITUITARY GLAND | N | N | N | N | N | N | N | N | N | N |
| CERVICAL CORD | N | N | N | N | N | N | N | N | N | N |
| THYMUS | N | | N | N | N | N | N | N | N | N |
| Hemorrhage, multifocal | - | 1 | - | - | - | - | - | - | - | - |
| SALIVARY GLAND | N | N | N | N | N | N | N | N | N | N |
| PANCREAS | N | N | N | N | | N | N | N | N | N |
| Hyperplasia, islet cell | - | - | - | - | 1 | - | - | - | - | - |
| MID-THORACIC CORD | N | N | N | N | N | N | N | N | | N |
| Chromatolysis, neuron | - | - | - | - | - | - | - | - | 1 | - |
| ADRENAL GLAND | | N | | N | N | N | N | | | |
| Ectopic adrenal | 1 | - | - | - | - | - | - | - | 1 | - |
| Hypertrophy, cortex, multifocal | 1 | - | 1 | - | - | - | - | 1 | 1 | 1 |
| LUMBAR CORD | N | N | N | N | N | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N | N | N | N | N | N |
| PARATHYROID GLAND | N | N | N | U | N | N | N | N | U | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| HEART | N | | | | N | | N | | | |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

| ANIMAL ID: | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | N | | | | N | | N | | | |
| Inflammation, chronic, multifocal | – | 1 | 1 | 1 | – | 1 | – | 1 | 1 | 1 |
| AORTA | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| COLON | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| LIVER | | | N | N | | | | | | |
| Inflammation, chronic, multifocal | 1 | 1 | – | – | 1 | 1 | 1 | 1 | 1 | 1 |
| SPLEEN | N | N | N | N | N | N | N | N | N | N |
| JEJUNUM | N | N | N | N | N | N | N | N | N | N |
| LUNG | | | | | | | N | N | | |
| Mineralization, intrinsic artery | 1 | – | – | – | – | – | – | – | – | 1 |
| Inflammation, acute, perivascular | 1 | 1 | 2 | 1 | 1 | 1 | – | – | – | 2 |
| Inflammation, chronic, interstitium | – | 1 | – | – | – | – | – | – | – | – |
| Inflammation, pyogranulomatous, focal | – | 1 | 1 | – | 1 | 1 | – | – | 1 | – |
| Hemorrhage | – | – | – | – | 1 | – | – | – | 1 | – |
| KIDNEY | | | N | | | | | | | |
| Inflammation, chronic, cortex | – | 1 | – | – | 1 | – | 1 | – | – | – |
| Nephropathy, progressive | 1 | 1 | – | – | – | – | – | 1 | – | – |
| Mineralization | 2 | 2 | – | 1 | 1 | 1 | 1 | 2 | 1 | 1 |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |
| SKIN (EXPOSURE AREA) | | | | N | | | | | N | |
| Hyperkeratosis | 1 | 1 | 1 | – | 1 | 1 | 1 | 1 | – | 1 |
| Acanthosis | – | – | – | – | – | 1 | – | – | – | – |

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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

| ANIMAL ID: | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 |
|---|---|---|---|---|---|---|---|---|---|---|
| SKIN (NON-EXPOSURE AREA) | N | | N | N | N | N | N | N | N | N |
| Hyperkeratosis | - | 1 | - | - | - | - | - | - | - | - |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N |
| ILEUM | N | N | N | N | N | N | N | N | N | N |
| CECUM | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC | N | N | N | N | N | N | N | N | N | N |
| SKELETAL MUSCLE | N | N | N | N | N | N | N | N | N | N |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| RECTUM | N | N | N | N | N | N | N | N | N | N |
| OVARY | N | N | N | N | N | N | N | N | N | N |
| UTERUS | N | N | N | | N | | | | | N |
| Dilatation | - | - | - | 1 | - | 3 | 1 | 2 | 3 | - |
| VAGINA | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| FEMUR | N | N | N | N | N | N | N | N | N | N |
| STERNUM | N | N | N | N | N | N | N | N | N | N |
| BONE MARROW | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | | | N | |
| Inflammation, subacute, periorbital | - | - | - | - | - | - | 1 | 1 | - | 1 |

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## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: FEMALE

| ANIMAL ID: | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 |
|---|---|---|---|---|---|---|---|---|---|---|
| LACRIMAL GLAND | N | N | | N | | N | N | N | N | N |
| Inflammation, chronic | - | - | 1 | - | 1 | - | - | - | - | - |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hyperplasia, lymphoid | - | - | - | - | 2 | - | - | - | - | - |
| Accumulation, plasma cell | - | 2 | - | - | - | - | - | - | - | - |

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## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 2
SEX: FEMALE

| ANIMAL ID: | 331 | 332 | 333 | 334 | 335 | 336 | 337 | 338 | 339 | 340 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | | | | | | N | N | | | N |
| Cyst | 1 | - | - | - | - | - | - | - | - | - |
| Inflammation, chronic, cortex | 1 | - | 1 | 1 | - | - | - | - | - | - |
| Nephropathy, progressive | - | - | - | 1 | - | - | - | - | - | - |
| Mineralization | 1 | 2 | - | 1 | 1 | - | - | 1 | 1 | - |
| SKIN (EXPOSURE AREA) | N | N | | | N | N | N | | N | N |
| Hyperkeratosis | - | - | 1 | 1 | - | - | - | 1 | - | - |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hyperplasia, lymphoid | - | - | - | 2 | - | - | - | - | - | - |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: FEMALE

| ANIMAL ID: | 351 | 352 | 353 | 354 | 355 | 356 | 357 | 358 | 359 | 360 |
|---|---|---|---|---|---|---|---|---|---|---|
| SALIVARY GLAND | N | | | | | | | | | |
| KIDNEY | | | | N | | | | | | |
| Dilatation, pelvis | 1 | - | - | - | - | - | - | - | - | - |
| Inflammation, chronic, cortex | - | - | - | - | - | 1 | - | - | - | 1 |
| Nephropathy, progressive | - | 1 | 1 | - | - | - | - | - | - | - |
| Mineralization | - | 1 | - | - | 1 | - | 1 | 1 | 1 | 1 |
| SKIN (EXPOSURE AREA) | N | N | N | | | N | | N | N | |
| Hyperkeratosis | - | - | - | 1 | 1 | - | 1 | - | - | 1 |
| SCIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| EAR | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MANDIBULAR | | | | | | | | | | |
| Hyperplasia, lymphoid | - | 3 | - | - | - | - | - | - | - | - |
| Accumulation, plasma cell | - | 2 | - | - | - | - | - | - | - | - |

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 4
SEX: FEMALE

| ANIMAL ID: | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 | 380 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAIN | N | N | | N | N | N | N | | N | |
| Dilatation, ventricle | - | - | 1 | - | - | - | - | 1 | - | 1 |
| PITUITARY GLAND | N | N | N | N | N | N | N | N | N | N |
| CERVICAL CORD | N | N | N | N | N | N | N | N | N | N |
| THYMUS | N | | N | N | N | N | N | | N | |
| Hemorrhage, multifocal | - | 1 | - | - | - | - | - | 1 | - | 1 |
| SALIVARY GLAND | N | N | N | N | N | N | N | | N | N |
| Inflammation, chronic | - | - | - | - | - | - | - | 1 | - | - |
| PANCREAS | N | N | N | N | N | N | N | N | | N |
| Atrophy, acinar | - | - | - | - | - | - | - | - | 1 | - |
| MID-THORACIC CORD | N | N | N | N | N | N | N | N | N | N |
| ADRENAL GLAND | N | | | N | N | N | N | N | | |
| Hypertrophy, cortex, multifocal | - | 1 | 1 | - | - | - | - | - | 1 | 1 |
| LUMBAR CORD | N | N | N | N | N | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N | N | N | N | N | N |
| PARATHYROID GLAND | N | N | N | U | N | N | N | N | N | U |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| HEART | | N | N | N | | N | | N | | |
| Inflammation, chronic, multifocal | 1 | - | - | - | 1 | - | 1 | - | 1 | 2 |
| AORTA | N | N | N | N | N | N | N | N | N | N |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

| ANIMAL ID: | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 | 380 |
|---|---|---|---|---|---|---|---|---|---|---|
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| COLON | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| LIVER | | | N | | | | | | | N |
| Inflammation, chronic, multifocal | 1 | 1 | - | 1 | 1 | 1 | 1 | 1 | 1 | - |
| SPLEEN | N | N | N | N | N | N | N | N | N | N |
| JEJUNUM | N | N | N | N | N | N | N | N | N | N |
| LUNG | | N | | | | N | | | | |
| Mineralization, intrinsic artery | - | - | - | 1 | - | - | - | - | 1 | - |
| Inflammation, acute, perivascular | - | - | 1 | 1 | 1 | - | 1 | 1 | 1 | - |
| Inflammation, chronic, interstitium | - | - | - | - | - | - | 1 | - | - | - |
| Inflammation, pyogranulomatous, focal | 1 | - | 1 | 1 | 1 | - | - | 1 | - | 1 |
| Hemorrhage | - | - | - | - | 1 | - | - | 1 | 1 | 1 |
| KIDNEY | | N | | | | | | | | |
| Inflammation, chronic, cortex | 1 | - | - | - | 1 | 1 | 1 | 1 | 1 | - |
| Nephropathy, progressive | - | - | - | 1 | - | 1 | - | - | - | 1 |
| Mineralization | - | - | 1 | 1 | 1 | 1 | 1 | - | 2 | 1 |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |
| SKIN (EXPOSURE AREA) | | | | | N | | N | | | |
| Hyperkeratosis | 1 | 1 | 1 | 1 | - | 1 | - | 1 | 1 | 1 |
| Acanthosis | 1 | - | - | - | - | 1 | - | 2 | 1 | - |
| SKIN (NON-EXPOSURE AREA) | N | N | N | N | N | N | N | N | N | N |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

| ANIMAL ID: | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 | 380 |
|---|---|---|---|---|---|---|---|---|---|---|
| LEUM | N | N | N | N | N | N | N | N | N | N |
| ECUM | N | N | N | N | N | N | N | N | N | N |
| YMPH NODE, MESENTERIC | N | N | N | N | N | N | N | N | N | N |
| KELETAL MUSCLE | N | N | N | N | N | N | N | N | N | N |
| CIATIC NERVE | N | N | N | N | N | N | N | N | N | N |
| ECTUM | N | N | N | N | N | N | N | N | N | N |
| VARY | N | N | N | N | N | N | N | N | N | N |
| TERUS | N | | N | N | N | N | N | N | N | N |
| Dilatation | - | 2 | - | - | - | - | - | - | - | - |
| AGINA | N | N | N | N | N | N | N | N | N | N |
| AR | N | N | N | N | N | N | N | N | N | N |
| EMUR | N | N | N | N | N | N | N | N | N | N |
| TERNUM | N | N | N | N | N | N | N | N | N | N |
| ONE MARROW | N | N | N | N | N | N | N | N | N | N |
| YE | N | N | | | N | N | | N | | |
| Inflammation, subacute, periorbital | - | - | 2 | 1 | - | - | 1 | - | 1 | 2 |
| ACRIMAL GLAND | N | N | N | N | N | | N | | | N |
| Inflammation, chronic | - | - | - | - | - | 1 | - | 1 | 1 | - |

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# SECTION V

# CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

Animal ID: 301
Animal Fate: Scheduled sacrifice

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| THYMUS - LESION, MOTTLED | THYMUS - Hemorrhage, multifocal |

Animal ID: 306
Animal Fate: Scheduled sacrifice

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| THYMUS - LESION, MOTTLED | THYMUS - Hemorrhage, multifocal |

Animal ID: 307
Animal Fate: Scheduled sacrifice

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| LYMPH NODE, MANDIBULAR - LESION, 4 MM X 2 MM, RED | LYMPH NODE, MANDIBULAR - Hemorrhage |

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AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 2
SEX: MALE

Animal ID: 321
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YMPH NODE, MANDIBULAR - ENLARGED, 5 MM X 12 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

Animal ID: 326
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YE - RIGHT, PIGMENTATION, RED

Related Histopathology:
EYE - Hemorrhage, periorbital

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: MALE

Animal ID: 341
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - LESION, 2 MM X 3 MM, RED

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hemorrhage

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FOUR WEEK TOXICITY STUDY OF WR279396
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TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

Animal ID: 362
Animal Fate: Scheduled sacrifice

| eference to Necropsy Record: | Related Histopathology: |
|---|---|
| YMPH NODE, MANDIBULAR - LESION, 4 MM X 2 MM, RED | LYMPH NODE, MANDIBULAR - Hemorrhage |
| DRENAL GLAND - LEFT, FOCUS, RED | ADRENAL GLAND - Hypertrophy, cortex, multifocal |

Animal ID: 367
Animal Fate: Scheduled sacrifice

| eference to Necropsy Record: | Related Histopathology: |
|---|---|
| YMPH NODE, MANDIBULAR - ENLARGED, 9 MM X 7 MM | LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid |

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

Animal ID: 312
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 8 MM X 5 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Accumulation, plasma cell

Animal ID: 315
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 13 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

Animal ID: 319
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
EYE - LEFT, LESION, OPAQUE

Related Histopathology:
EYE - No corresponding lesion

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 2
SEX: FEMALE

Animal ID: 334
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 7 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: FEMALE

Animal ID: 351
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
SALIVARY GLAND - LESION, RED

Related Histopathology:
SALIVARY GLAND - No corresponding lesion

Animal ID: 352
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 12 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

## CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

No Gross Observations for any animal in this group

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# SECTION VI

# QUALITY ASSURANCE STATEMENT

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## QUALITY ASSURANCE STATEMENT

This histopathology project was inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) standards promulgated by the U.S. Food and Drug Administration. The pathology 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 and Study Pathologist |
|---|---|---|---|
| * | 05/31/95 | Tissue Trimming | 06/01/95 |
| * | 04/27/95 | Processing/Embedding | 04/27/95 |
| ** | 04/06/95 | Microtomy | 04/06/95 |
| * | 04/27/95 | Staining | 04/27/95 |
| * | 04/27/95 | Coverslipping | 04/27/95 |
| * | 01/05/95 | Labeling | 01/05/95 |
| * | 04/06/95 | Quality Control/Checkout | 04/06/95 |
| ** | 06/14/95 | Individual Animal Data | 06/14/95 |
| ** | 06/14/95 | Computer Generated Tables | 06/14/95 |
| ** | 06/14/95 | Draft Pathology Report | 06/14/95 |
| ** | 09/13/95 | Final Pathology Report | 09/13/95 |
| ** | 09/28/95 | Amended Final Pathology Report | 09/28/95 |

* General quarterly phase inspection
** Inspection specific for this study

In accordance with the PAI Quality Assurance Division's Standard Operating Procedures, all critical phase inspections are conducted on a random basis quarterly or more frequently. Those general phase inspections listed are the most recent conducted during the period each task associated with this project was performed.

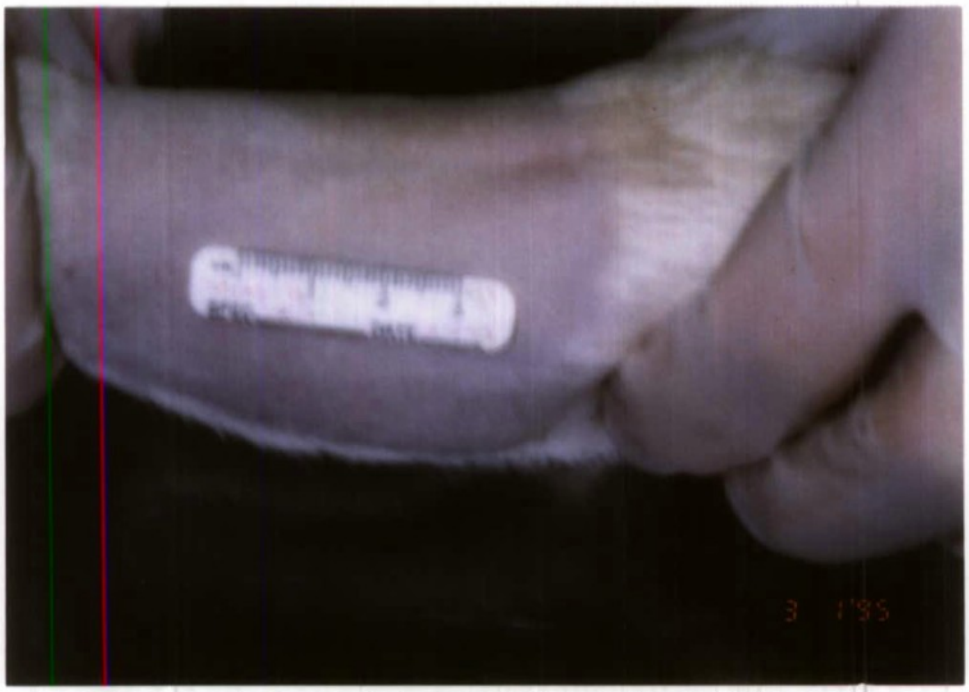
Andrea M. Smith
Quality Assurance Unit
PAI Illinois Division

09/28/95
Date

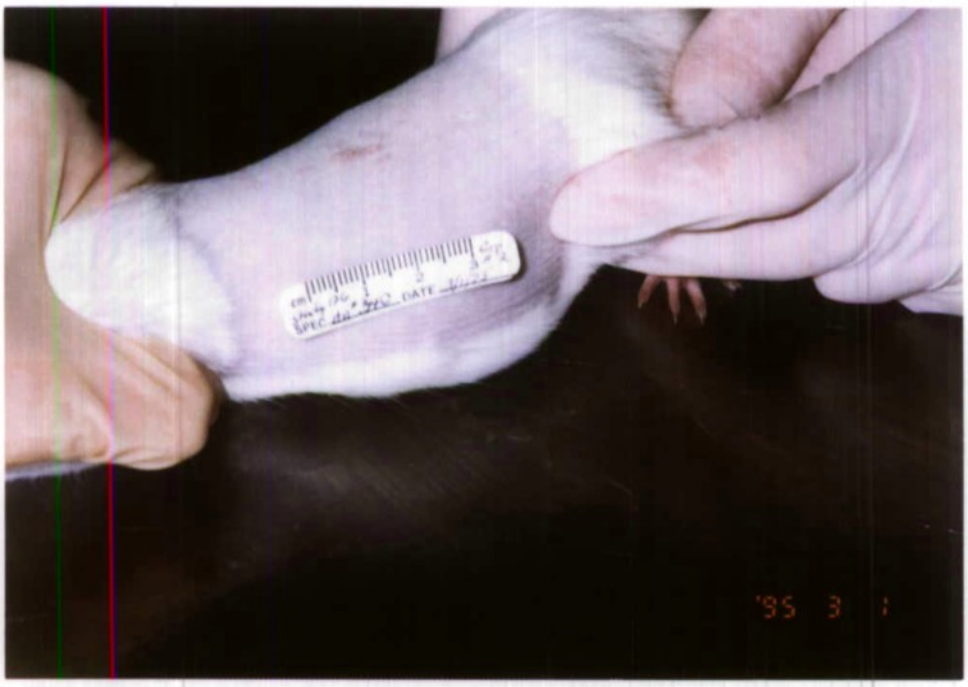
Four Week Toxicity Study of WR279396 After Daily Dermal Application in CD® Rats
UIC/TRL Study Number 176

# APPENDIX 10

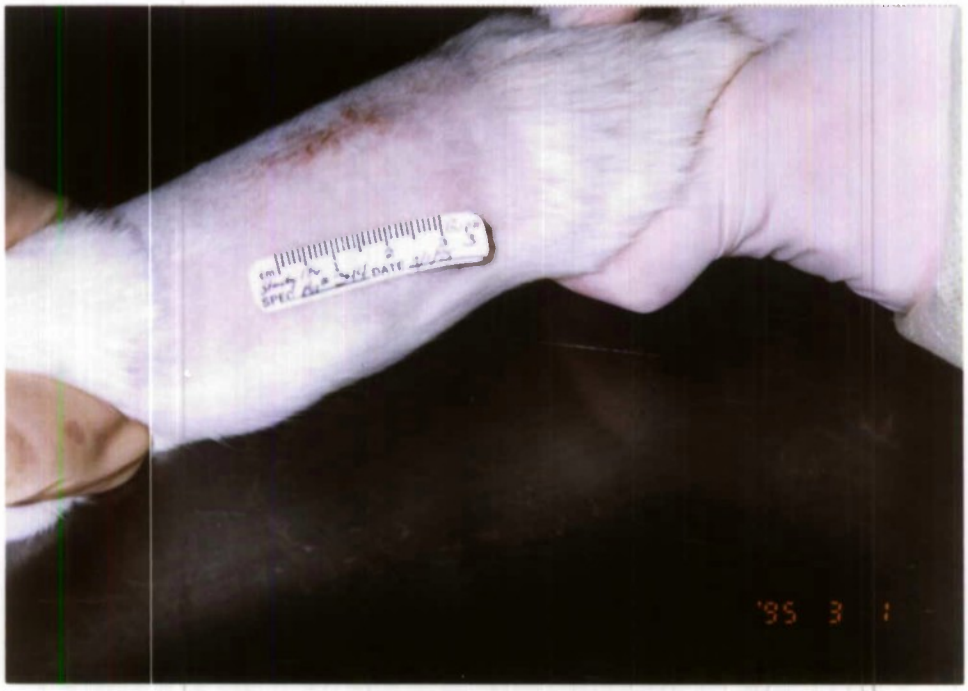
# PHOTOGRAPHS OF TREATMENT SITES ON DAY 6



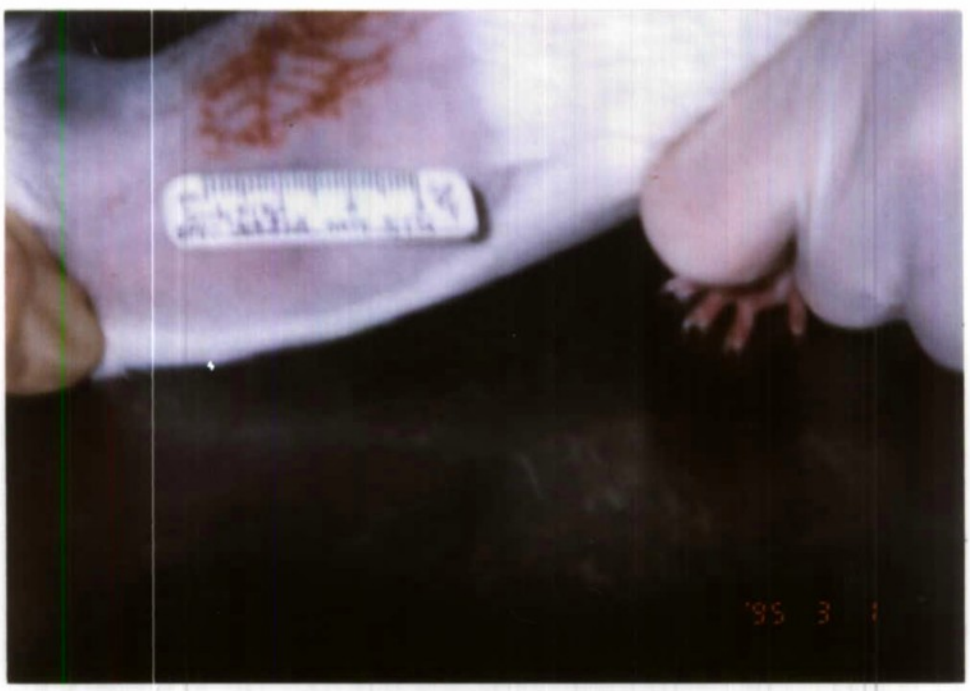
Study Day: 6
Animal No.: 313 Sex: Female
Dosing Volume: 1.67 ml/kg/day x 2 Vehicle Control



Study Day: 6
Animal No.: 340 Sex: Female
Dosing Volume: 0.07 ml/kg/day x 2 WR279396



Study Day: 6
Animal No.: 344 Sex: Male
Dosing Volume: 0.33 ml/kg/day x 2 WR279396



Study Day: 6
Animal No.: 372 Sex: Female
Dosing Volume: 1.67 ml/kg/day x 2 WR279396

# APPENDIX 11

# PROTOCOL AND PROTOCOL AMENDMENTS

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

## 1.0 PURPOSE OF THE STUDY:

The objective of this study is to determine the local and systemic (organ) toxicity of WR279396 in CD® rats following four weeks of daily dermal application. WR279396 (Iowa Formulation 232) is a cream containing 0.5% gentamicin sulfate and 15% paromomycin sulfate, which is being developed for use against cutaneous leishmaniasis. 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<br>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)<br>Department of Pharmacology<br>1940 W. Taylor St.<br>Chicago, Illinois 60612-7353 |
| 3.3 | Study Director: | Barry S. Levine, D.Sc., D.A.B.T. |

## 4.0 DATES:

| | | |
|---|---|---|
| 4.1 | Proposed Initiation of Dosing: | 02/23/95 |
| 4.2 | Proposed Necropsy Dates: | 03/23-24/95 |
| 4.3 | Proposed Study Completion Date (Draft Study Report): | 06/23/95 |



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## 5A.0 TEST ARTICLE

5A.1 Name or Code No: WR279396 [0.5% gentamicin sulfate- and 15% paromomycin sulfate-containing cream (Iowa Formulation 232)]

5A.2 TRL Chemical No: 1980614

5A.3 Physical Description: White cream. The specific gravity is ≈1.0, as indicated by the Sponsor.

5A.4 Stability and Handling of Test Article:

5A.4.1 Storage Conditions to Maintain Stability:

5A.4.1.1 Temperature: 2 - 8°C.

5A.4.1.2 Humidity: Ambient conditions at 2 - 8°C.

5A.4.1.3 Light: Protect from light; opaque bottle.

5A.4.1.4 Special Requirements: None.

5A.4.2 Special Handling Procedures: Standard safety precautions including gloves, eye protection, mask and labcoat.

5A.4.3 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, all unused test article will be returned to the Sponsor if requested.

## 5B.0 PLACEBO (VEHICLE)

5B.1 Name or Code No: Iowa Formulation 232 without either gentamicin sulfate or paromomycin sulfate (vehicle).

5B.2 TRL Chemical No: 1990614

5B.3 Physical Description: White cream. The specific gravity is ≈1.0, as indicated by the Sponsor.

5B.4 Stability and Handling of Placebo (Vehicle):

5B.4.1 Storage Conditions to Maintain Stability:



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5B.4.1.1 Temperature: 2 - 8°C.

5B.4.1.2 Humidity: Ambient conditions at 2 - 8°C.

5B.4.1.3 Light: Protect from light; opaque bottle.

5B.4.1.4 Special Requirements: None.

5B.4.2 Special Handling Procedures: Normal safety procedures will be used including labcoats, masks, eye protection, and gloves.

5B.4.3 Log of Placebo (Vehicle): The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the control article was removed from the batch will be documented. At termination of the study, all unused control article will be returned to Sponsor if requested.

## 6.0 PERSONNEL:

| | |
|---|---|
| Study Director | Barry S. Levine, D.Sc., D.A.B.T. |
| Toxicologist | Clyde W. Wheeler, Ph.D. |
| Pathologist | Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P. |
| Clinical Veterinarian | James Artwohl, D.V.M., M.S., D.A.C.L.A.M. |
| Veterinarian Support | Documented in the raw data |
| Ophthalmologist | Samuel J. Vainisi, D.V.M., D.A.C.V.O. |
| Clinical Laboratory | Maria Lang, A.H.T., C.V.T. |
| Tox. Lab Supervisor | Soudabeh Soura, B.S. |
| Lead Technician | Documented in raw data |
| Quality Assurance | Ronald C. Schoenbeck |

## 7.0 TEST SYSTEM:

| | | |
|---|---|---|
| 7.1 | Species: | Rat |
| 7.2 | Strain: | CD® (Virus Antibody Free) |
| 7.3 | No. and Sex(s): | 40 males and 40 females |
| 7.4 | Age of Animals: | Approximately 7 weeks old at dosing initiation. |
| 7.5 | Weight of Animals: | Approximately 200 - 250 g (males) and approximately 175 - 200 g (females) at dosing initiation. |



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7.6 Source of Animals: Charles River Breeding Laboratories. Kingston, NY.

7.7 Justification for Selection of Test System: The FDA requires the use of two animal species in preclinical toxicology studies. The rat is a standard and accepted rodent species for toxicology studies, and is specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Upon arrival, each animal will be given a study-unique quarantine/pretest number. During the test animal selection process, each test animal will be assigned a test animal number unique to it within the population making up the study. This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It 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 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 one week. During that time, the animals will be observed daily for signs of illness, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly 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 or Toxicologist. 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, 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 the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.



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## 8.0 EXPERIMENTAL DESIGN:

### 8.1 Treatment Groups:

| Treatment Group | Treatment | Paromomycin Dose Level (mg/kg/day) | Gentamicin Dose Level (mg/kg/day) | Dosing Volume (ml/kg/day) | Number of Males | Number of Females |
|---|---|---|---|---|---|---|
| 1 | Vehicle | 0 | 0 | 1.67 x 2 (1.67) | 10 | 10 |
| 2 | WR279396 | 20 (10) | 0.7 (0.04) | 0.07 x 2 (0.07) | 10 | 10 |
| 3 | WR279396 | 100 (50) | 3.3 (1.7) | 0.33 x 2 (0.33) | 10 | 10 |
| 4 | WR279396 | 500 (250) | 16.7 (8.4) | 1.67 x 2 (1.67) | 10 | 10 |

Dose levels were selected following discussions with the Sponsor. They were chosen on the basis of the amount of paromomycin which will be administered to patients although both paromomycin and gentamicin will be administered. As indicated by the Sponsor, the intended routine clinical dose of paromomycin is 5 mg/kg/day. As such, a low dose in this study of 20 mg/kg/day allows for a four-fold margin of safety. It was further stated by the Sponsor that the maximum clinical dose for a severely infected individual would be 50 mg/kg/day. Accordingly, the present mid dose affords a two-fold safety factor over this worst case scenario clinical dose. The high dose level in this study of 500 mg/kg/day (1.67 ml WR279396/kg/application) is intended to result in toxicity and is near the typical upper limit of dermal dosing of 2 ml/kg/application.

Because moderate to severe erythema was seen in high and mid dose animals on day 5, the initial dose levels were reduced by one-half. The new dose levels of paromomycin and gentamicin are shown above in parentheses. This will be accomplished by reducing the frequency of dosing from twice daily to once daily. The dosing volume per application will remain constant.

The number of animals 10/sex/group, is necessary for adequate statistical analysis, and is routinely used in rodent regulatory toxicology studies. This number of animals is also indicated in the 1993 *OECD Guidelines for Testing of Chemicals;* Repeated Dose Dermal Toxicity: 21/28 Day Study. No such FDA document exists for the testing of drugs.

8.2 Frequency and Route of Administration of the Test Article: The FDA requires toxicology testing for at least twice the duration of clinical testing to support a Phase III clinical trial of WR279396 which will be clinically tested against cutaneous leishmaniasis for no more than 10 days. The current 28-day dermal toxicology study will provide the clinicians with a 4-day safety net in case the duration of clinical treatment must be extended.

The test article will be applied by the dermal route twice daily for four weeks. The fur



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on the back of each test animal will be clipped approximately 24 hours prior to initial test article application. An area approximately 7 cm long and extending approximately 3 cm on both sides of the midline will be exposed, and will constitute the dosing area. Only animals with healthy intact skin will be used. The backs will be reshaved during the course of the study as necessary.

The animals will be fitted with a jacket for dermal applications during week -1. Immediately prior to the initial treatment on day 0 and weekly thereafter unless fissuring is observed, the animals will have the dosing area abraded by cross-hatched cuts made with a detached size 10 electric clipper blade so that the stratum corneum is penetrated but the dermis is left intact. The test article will be administered using a 1 ml tuberculin syringe (0.01 ml graduations) and uniformly applied as a thin film over the exposure area of the skin (up to $\approx$ 10% of the total body surface area) twice daily, approximately 3 - 4 hours apart, for at least 28 consecutive days. The specific volume to be administered (to the nearest 0.01 ml) will be adjusted on the basis of each animal's most recent body weight. The material will be initially applied to a latex gloved finger, which will be used to uniformly apply the test article to the exposure area of the skin. A separate gloved finger will be used for each animal, i.e. after dosing up to four rats, the glove will be discarded, and a new latex glove will be donned. The application site will be left uncovered. Approximately 3 - 4 hours after the last daily application, the exposure site will be wiped with a water-moistened paper towel and the animal jackets will be removed and left off overnight. The animals will be dosed up to and including the day prior to scheduled necropsy on day 28 or 29.

8.3 Justification of Route: Dermal application is the intended clinical route and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, the animals will be randomized separately by sex into the groups shown in Section 8.1 using a computer-generated randomization procedure on the basis of body weight.

8.5 Test Article Dosage Form Preparation and Analyses: The test article will be administered undiluted. Homogeneity, stability and test article concentration analyses will not be conducted by UIC/TRL, and are the responsibility of the Sponsor.

8.6 Type and Frequency of Observations, Tests, Analyses and Measurements:

8.6.1 Clinical Signs: All animals will be observed twice daily $\approx$ 1 - 2 hours after each dermal application for clinical signs of toxicity. Additionally, all animals will be observed for moribundity/mortality in the morning.

8.6.2 Clinical Observations: All animals will be subjected to a physical examination including examination of eyes and all orifices at randomization (Week -1), on day 0 and weekly thereafter.



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8.6.3 Evaluation of Dermal Irritation: Dermal irritation will be evaluated once weekly prior to the first daily dose. The draize dermal irritation scoring procedure will be employed (Draize, J.H., 1965; Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics; Association of Food and Drug Officials of the U.S., Austin, TX).

Erythema and eschar formation:

| | |
|---|---|
| No erythema | 0 |
| Very slight erythema (barely perceptible) | 1 |
| Well defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema (beet redness) to slight eschar formation (injuries in depth) | 4 |

Edema formation:

| | |
|---|---|
| No edema | 0 |
| Very slight edema (barely perceptible) | 1 |
| Slight edema (edges of area well defined by definite raising) | 2 |
| Moderate edema (raised approximately 1.0 mm) | 3 |
| Severe edema (raised more than 1.0 mm and extending beyond the exposure area) | 4 |

8.6.4 Body Weight: Body weights of all animals will be recorded at randomization in week -1, on day 0 and weekly thereafter.

8.6.5 Food Consumption: Food consumption for all animals will be measured weekly commencing in week -1.

8.6.6 Clinical Pathology: Hematology and clinical chemistry parameters will be measured on days 27 and 28 (one day prior to necropsy). The animals will be anesthetized by inhalation of $CO_2$:$O_2$ (80:20), and approximately 1.5 - 2.0 ml of blood will be collected from the orbital sinus to measure the following parameters. The samples will be processed in the same random order as collected.



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Hematology

| | |
|---|---|
| Erythrocyte count and morphology | Mean corpuscular volume (MCV) |
| Hematocrit | Mean corpuscular hemoglobin (MCH) |
| Hemoglobin | Mean corpuscular hemoglobin concentration (MCHC) |
| Leukocyte count, total and differential | Platelet count |
| | [a]Reticulocyte count |

[a]Slides will be prepared, but will not be evaluated unless signs of anemia are present.

Clinical Chemistry

| | |
|---|---|
| Alanine aminotransferase (ALT) | Glucose |
| Albumin | Globulin (calc.) |
| Alkaline phosphatase | Phosphorus, inorganic |
| Bile acids, total | Potassium |
| Calcium | Protein, total |
| Chloride | Sodium |
| Cholesterol | Sorbitol dehydrogenase |
| Creatinine | Urea nitrogen (BUN) |

8.6.7 Ophthalmologic Examinations: All animals will be examined by indirect ophthalmoscopy prior to study initiation and in week 4.

8.6.8 Pathology: All animals which die on test or are sacrificed if moribund will be necropsied on the day of death. Surviving animals will be killed and necropsied in random order on days 28 and 29. Animals will be anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and will then be perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy will then be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice.

The necropsy procedure will be a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin.



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*Adrenal glands
Aorta
*Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Gross lesions
*Heart
Ileum
Jejunum
*Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
*Liver
*Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
*Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic and lumbar)
*Spleen
Sternum with bone marrow
Stomach
*Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina

*Weighed at scheduled necropsy (paired organs will be weighed as a unit).

All tissues collected at necropsy will be examined microscopically in all control and high dose animals. In addition, animals found dead or subjected to a moribund kill may be processed for microscopic examination following consultation with the Sponsor. All gross lesions will be examined microscopically. The kidneys, ears and sciatic nerve, and any other target organs identified in high dose animals, will be examined in low and mid dose animals.

8.6.9 Statistical Analyses: For each sex, Analysis of Variance tests will be conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analyses will consider weights relative to brain



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weight. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's t test will be used for pairwise comparisons to the control group. Frequency data such as incidence of mortality, gross necropsy observations and tissue morphology observations will be compared by Fishers Exact Test or Chi-square analyses as necessary.

8.6.10 Deliverables: Quantitative data will be tabulated and presented in the report. In addition to the written report, individual data in "ASCII" form and summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette). 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 as direct computer input, will be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that will be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output will be bound during or at the conclusion of the study. All data entries will 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) will be made so as not to obscure the original entry, will indicate the reason for such change, and will be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input will be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) will be made in such a manner so as not to obscure the original entry, if possible, will indicate the reason for such change, and will be dated and the responsible individual will be identified.

All recorded data will be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens (including histology and paraffin blocks of tissues) and other materials necessary to reconstruct the study will be stored in the TRL Archives maintained by Quality Assurance, unless otherwise specified by the Sponsor.

All changes or revisions, and reasons therefore, to this protocol once it is approved will be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol. Additionally, the Sponsor is to be notified immediately of any illness or problems which develop during the study. Should a protocol or SOP deviation occur, the circumstances, action taken (if any), and the impact on the study will be assessed immediately by the Study Director and documented on a Protocol Deviation form.

## 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.

Will this study be submitted to a regulatory agency? Yes
If so, to which agency(ies)? US Food and Drug Administration
Does the Sponsor request that remaining test and control articles be returned?
Possibly; see Sections 5A.4.3 and 5B.4.3
Does the Sponsor request that samples of the test article/carrier mixture(s) be sent to the Sponsor for analysis? Not applicable

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Barry S. Levine, D.Sc., D.A.B.T. — Date: 10/28/94

QUALITY ASSURANCE: Ronald Schoenbeck — Date: 10/28/94

SPONSOR APPROVAL: George Schieferstein, Ph.D., Contracting Officer's Representative (COR) — Date: 10/31/94.

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

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

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

Appendix 1

October 27, 1994

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

Dear Dr. Levine:

The modifications requested in your correspondence of October 20, 1994 pertaining to your approved protocol ACC: #93-031-19: "Four Week Dermal Toxicity Study of WR279396 in CD 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 October 26, 1994 and consequently the records of 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, Ph.D.
Chair, Animal Care Committee

MWL:st
xc: BRL

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

1. Page 1 Section 4.0

Add the study dates as follows:

| | | |
|---|---|---|
| 4.1 | Proposed Initiation of Dosing: | 02/23/95 |
| 4.2 | Proposed Necropsy Dates: | 03/23-24/95 |
| 4.3 | Proposed Study Completion Date (Draft Study Report): | 6/23/95 |

Reason: The study dates have been finalized.

2. Page 2 Section 5B.3

Include the physical description of the control article as a "White cream. The specific gravity is $\approx$ 1.0, as indicated by the Sponsor."

Reason: Physical description provided by the Sponsor upon receipt of the control article.

3. Page 4 Section 7.8

Replace the third sentence with the following: "This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It will also appear on a cage card visible on the front of each cage."

Reason: Clarification of the protocol. We have recently implemented the use of an implantable microchip identification system for use in GLP toxicology studies.

4. Page 5 Section 8.1

Add the redlined text to the table and insert the following paragraph after first paragraph.

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

4. (contd.)

| Treatment Group | Treatment | Paromomycin Dose Level (mg/kg/day) | Gentamicin Dose Level (mg/kg/day) | Dosing Volume (ml/kg/day) | Number of Males | Number of Females |
|---|---|---|---|---|---|---|
| 1 | Vehicle | 0 | 0 | 1.67 x 2 (1.67) | 10 | 10 |
| 2 | WR279396 | 20 (10) | 0.7 (0.04) | 0.07 x 2 (0.07) | 10 | 10 |
| 3 | WR279396 | 100 (50) | 3.3 (1.7) | 0.33 x 2 (0.33) | 10 | 10 |
| 4 | WR279396 | 500 (250) | 16.7 (8.4) | 1.67 x 2 (1.67) | 10 | 10 |

Because moderate to severe erythema was seen in high and mid dose animals on day 5, the initial dose levels were reduced by one-half. The new dose levels of paromomycin and gentamicin are shown above in parentheses. This will be accomplished by reducing the frequency of dosing from twice daily to once daily. The dosing volume per application will remain constant.

Reason: Because moderate to severe erythema was seen in mid and high dose animals on day 5, following consultation with the Sponsor, the dose levels were reduced by one-half as described above.

5. Page 6 Section 8.2

In the last paragraph, indicate that the jackets will be removed and left off the animals overnight following cleaning of the exposure site after the last daily application.

Reason: Clarification of the protocol.

6. Page 7 Section 8.6.6

Change when blood will be collected for the measurement of clinical pathology parameters to "days 27 and 28 (one day prior to necropsy)" from "at scheduled termination on days 28 and 29".

Reason: Clarification of the protocol. Logistics prevent the performance of blood collection for clinical pathology determinations and the whole animal perfusion for tissue fixation on the necropsy day.

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

7. Page 8 Section 8.6.8

Replace the first paragraph with the following: "All animals which die on test or are sacrificed if moribund will be necropsied on the day of death. Surviving animals will be killed and necropsied in random order on days 28 and 29. Animals will be anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and will then be perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy will then be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice."

Reason: The means of euthanasia was changed and transcardial perfusion with NBF was added to insure the proper fixation of the neural tissues.

8. Page 9 Section 8.6.8

A. Remove "Bone marrow smear (femur)" from tissue list.

B. Remove reference to bone marrow smears in first paragraph and delete second paragraph.

Reason: Because the animals are being whole body perfused with 10% neutral buffered formalin at necropsy, bone marrow smears can not be obtained.

Approvals:

STUDY DIRECTOR: _____ 3/14/95
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 3/15/95.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

9. Page 1 Title

Change the Study Title to "FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS" from "FOUR WEEK DERMAL TOXICITY STUDY OF WR279396 IN CD® RATS".

Reason: Sponsor requested change in the protocol and in the resulting study report.

10. Page 2 Section 5B.0

Change the designation of the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate to "PLACEBO (VEHICLE)" from "CONTROL ARTICLE".

Reason: Sponsor requested change in the protocol and in the resulting study report.

11. Page 2 Section 5B.4

Replace "Stability and Handling of Control Article" with "Stability and Handling of Placebo (Vehicle)".

Reason: Sponsor requested that the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate be designated as the "Placebo (Vehicle)".

12. Page 2 Section 5B.4.3

Replace "Log of Control Article" with "Log of Placebo (Vehicle)".

Reason: Sponsor requested that the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate be designated as the "Placebo (Vehicle)".

Approvals:

STUDY DIRECTOR: Barry S. Levine, D.Sc. D.A.B.T. — Date: 9/21/95

SPONSOR APPROVAL: George J. Schieferstein, Ph.D. Contracting Officer's Representative (COR) — Date: 9/20/95

# APPENDIX 12

# STUDY DEVIATIONS

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

# FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

## Study Deviations*

| Deviation Type | Specific Deviation | Effect on Study |
|---|---|---|
| Protocol | On a few occasions, the temperature and/or relative humidity deviated outside the specified ranges in the animal room. The temperature and relative humidity deviations ranged from -2 to +2°F and -3 to +0%, respectively, outside the specified ranges. | None. These deviations were sporadic. |
| Protocol | Reticulocyte count was determined in the absence of signs of anemia. | None. |
| Protocol | Animals were anesthetized by inhalation of $CO_2$:$O_2$ (70:30) instead of $CO_2$:$O_2$ (80:20). | None. |
| Protocol | Parathyroids (7) and mammary gland (1) were not evaluated histologically in a few high dose and control animals. Parathyroids and mammary glands are inherently difficult to obtain in sections because of their size. These tissues were recorded as "unsuitable for complete evaluation" since they were missing in both the original section and in the recut and retrim attempts to obtain them. | None. Treatment-related lesions were not seen in these tissues. |

*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.

Barry S. Levine, D.Sc., D.A.B.T.

10/3/95
Date