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CEDRA DCN 11-657-T1

Mylan Pharmatceuticals Inc. PRIL-0367

Protocol



Mylan Pharmaceuticals, Inc. PRIL-0367 PRACS R03-726	VER: 10-13-03 Carlson
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**A RELATIVE BIOAVAILABILITY STUDY COMPARING 20 MG PRILOSEC[®] OTC TABLETS
VERSUS 20 MG PRILOSEC[®] CAPSULES UNDER FASTING CONDITIONS**

COPY

STUDY SPONSOR:

Russ Rackley, Ph.D.
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

(304) 598-5430

CLINICAL INVESTIGATOR:

James D. Carlson, Pharm.D.
PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

(701) 239-4750

ANALYTICAL FACILITY:

CEDRA Corporation
8609 Cross Park Drive
Austin TX 78754

(856) 216-9683

PRACS INSTITUTIONAL REVIEW BOARD:

Chairman: William Henderson, Ph.D.
3014 Elm Street
Fargo, ND 58102

(701) 293-9609

Study Dates: Period I: OPEN
Period II: OPEN

Number of Study Subjects: Forty-eight and No Alternates

Study Products:

Test Product - 20 mg PRILOSEC[®] OTC Tablets distributed by Procter & Gamble
Reference Product - 20 mg PRILOSEC[®] Capsules manufactured for AstraZeneca LP by Merck & Co. Inc.

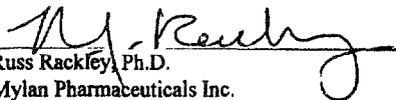
Protocol Print Dates: October 13, 2003
October 7, 2003
September 26, 2003



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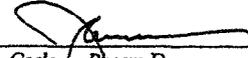
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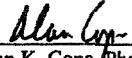
10/15/03
Date

CLINICAL INVESTIGATOR:



James D. Carlson, Pharm.D.
Principal Investigator
PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

10/13/03
Date



Alan K. Copa, Pharm.D.
Sub-Investigator
PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

10/13/03
Date

ANALYTICAL INVESTIGATOR:



CEDRA Corporation
8609 Cross Park Drive
Austin TX 78754

10/13/03
Date

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STUDY ABSTRACT

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A. Study Design

1. Randomized, single-dose, two-way crossover study under fasting conditions
 - a. Forty-eight healthy volunteers and no alternates
2. Dosing Regimen:

Investigational Products: 20 mg of *test* PRILOSEC® OTC Tablets distributed by Procter & Gamble or 20 mg of *reference* PRILOSEC® Capsules manufactured for AstraZeneca LP by Merck & Co. Inc

 - a. Drug Regimen: Two dosing periods
 - (A) 1 tablet of *test* product with 240 mL of room temperature water after an overnight fast
 - (B) 1 capsule of *reference* product with 240 mL of room temperature water after an overnight fast
 - b. Washout: At least a 7 day washout between doses
3. Subject Evaluation:
 - a. Enrollment Screening: Acceptable medical history, medication history, physical examination, and electrocardiogram, selected routine clinical laboratory measurements and screens for HIV antibody, hepatitis B surface antigen, hepatitis C antibody, pregnancy (females only), and drugs of abuse
 - b. Study Exit: Physical examination, selected clinical laboratory measurements, and pregnancy screen (females only)
4. Study Procedures:
 - a. Food and fluid intake will be controlled during confinement.
 - b. Blood sampling. 25 samples per subject each period for drug content analysis; sampling should occur within one hour prior to dosing (0 hour) and after dose administration at:

0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, and 16 hours

- c. Blood samples collected within 2 minutes of scheduled time will not be considered protocol deviations.
- d. The blood samples will be collected in heparinized vacutainers, inverted 5-10 times immediately after collection, placed in an ice bath, centrifuged, and the plasma pipetted into duplicate amber polypropylene tubes, frozen and stored at -70°C ± 15°C until analysis. Upon study completion, the "A" plasma samples will be directed to the analytical laboratory for sample analysis. The duplicate "B" plasma samples will be shipped after confirmation of receipt for the "A" plasma samples. No shipment will occur without written consent from the Bioanalytical Laboratory Management at Mylan Pharmaceuticals.
5. Subject Safety: The subjects will be monitored throughout the confinement portion of the study. Blood pressure and heart rate will be measured prior to dosing and as scheduled following each dose.

B. Analytical Laboratory and Statistical Analysis

1. The omeprazole plasma will be measured using a validated analytical method.
2. The final report will include concentrations at each sampling time, the appropriate pharmacokinetic parameters and statistical analysis of the data.

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Omeprazole is indicated for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD). It is indicated for the short-term treatment of diagnostically confirmed erosive esophagitis (associated with GERD).

Omeprazole, in combination with clarithromycin and amoxicillin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

The peak concentration is 1.6 hours. The elimination half-life is 1-1.5 hrs.¹

II. OBJECTIVE

This study will compare the relative bioavailability (rate and extent of absorption) of 20 mg PRILOSEC® OTC Tablets distributed by Procter & Gamble with that of 20 mg PRILOSEC® Capsules manufactured for AstraZeneca LP by Merck & Co. Inc. following a single oral dose (1 x 20 mg) in healthy adult volunteers under fasting conditions.

¹ Drug Monograph: PRILOSEC® Medical Economics Data Production Company, Physician's Desk Reference® 57th ed., Montvale, New Jersey. 2003; pp 619-623
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III. INVESTIGATORS AND FACILITIES

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A. Clinical Research Investigators and Facilities:

James D. Carlson, Pharm.D., Principal Investigator
Alan K. Copa, Pharm.D., Sub-Investigator
PRACS Institute, Ltd.
Fargo, ND 58104 & East Grand Forks, MN 56721

Activities: Study management, on-site protocol activities, dosing, and sample collection

Craig R. Sprenger, M.D. Medical Investigator PRACS Institute, Ltd Fargo, ND 58104	Scott S. Harris, M.D. Medical Investigator PRACS Institute, Ltd Fargo, ND 58104	Thomas B. Cariveau, M.D. Medical Investigator MeritCare Clinic East Grand Forks, MN 56721
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Activities: Physical examination, medical record review and medical investigator on-site and on-call professional services

B. Clinical Laboratory Facilities:

Anthony Thomas, M.D.
Quest Diagnostics, Inc.
Wood Dale, IL 60191-1024

[Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody]

Victoria Leier, MT (ASCP)
PRACS Institute Clinical Laboratory
Fargo, ND 58104

[Hematology, Chemistry, Urinalysis, Drug Screen, Pregnancy Screen]

Activities: Certified reference clinical laboratories, clinical lab sample analysis

C. Analytical Facility:

CEDRA Corporation
8609 Cross Park Drive
Austin TX 78754

Activities: Quantitate plasma concentration data

D. Statistical Analysis:

CEDRA Corporation
8609 Cross Park Drive
Austin TX 78754

Activities: Calculation of pharmacokinetic and statistical parameters for the drug concentration data

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IV. EXPERIMENTAL PLAN

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A. Evaluation of Study Participants at Screening, Study Check-in and Study Exit

1. Source of Volunteers:

Subjects will be selected from non-institutionalized volunteers consisting of university students and members of the community at large.

2. Screening Inclusion Criteria for Study Subjects:

a. **Screening Demographics:** All volunteers selected for this study will be healthy men or women 18 years of age or older at the time of dosing. The weight range will not exceed $\pm 15\%$ for height and body frame as per Desirable Weights for Adults - 1983 Metropolitan Height and Weight Table.

b. **Screening Procedures:** Each volunteer will complete the screening process within 14 days prior to Period I dosing. Consent documents for both the screening evaluation and HIV antibody determination will be reviewed, discussed, and signed by each potential participant before full implementation of screening procedures.

Screening will include general observations, physical examination, demographics, medical and medication history, an electrocardiogram, sitting blood pressure and heart rate, respiratory rate and temperature. The physical examination will include, but may not be limited to, an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems.

The screening clinical laboratory procedures will include:

- **HEMATOLOGY:** hematocrit, hemoglobin, WBC count with differential, RBC count, platelet count;
- **CLINICAL CHEMISTRY:** serum creatinine, BUN, glucose, AST(GOT), ALT(GPT), albumin, total bilirubin, total protein, and alkaline phosphatase;
- **HIV antibody and hepatitis B surface antigen and hepatitis C antibody screens;**
- **URINALYSIS:** by dipstick; full microscopic examination if dipstick positive; and
- **URINE DRUG SCREEN:** ethyl alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates and phencyclidine.
- **SERUM PREGNANCY SCREEN (female volunteers only)**

c. If female and:

- of childbearing potential, is practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s), such as condoms, foams, jellies, diaphragm, intrauterine device (IUD) in place for at least 3 months prior to

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the study and remaining in place during the study, or abstinence;
or

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- is postmenopausal for at least 1 year; or
- is surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).

3. Screening Exclusion Criteria for Study Subjects:

- a. Volunteers with a recent history of drug or alcohol addiction or abuse.
- b. Volunteers with the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (as determined by the clinical investigators).
- c. Volunteers whose clinical laboratory test values are outside the accepted reference range and when confirmed on re-examination are deemed to be clinically significant
- d. Volunteers demonstrating a positive hepatitis B surface antigen screen, a positive hepatitis C antibody screen, or a reactive HIV antibody screen.
- e. Volunteers demonstrating a positive drug abuse screen when screened for this study.
- f. Female volunteers demonstrating a positive pregnancy screen.
- g. Female volunteers who are currently breastfeeding.
- h. Volunteers with a history of allergic response(s) to omeprazole or related drugs.
- i. Volunteers with a history of clinically significant allergies including drug allergies.
- j. Volunteers with a clinically significant illness during the 4 weeks prior to Period I dosing (as determined by the clinical investigators).
- k. Volunteers who currently use or report using tobacco products within 1 year of the study.
- l. Volunteers who have taken any drug known to induce or inhibit hepatic drug metabolism in the 28 days prior to Period I dosing.
- m. Volunteers who report donating greater than 450 mL of blood within 28 days prior to Period I dosing. All subjects will be advised not to donate blood for four weeks after completing the study.
- n. Volunteers who have donated plasma (e.g. plasmapheresis) within 28 days prior to Period I dosing. All subjects will be advised not to donate plasma for four weeks after completing the study.

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- o. Volunteers who report receiving any investigational drug within 30 days prior to Period I dosing.
- p. Volunteers who report taking any systemic prescription medication in the 14 days prior to Period I dosing.
- q. Volunteers who have taken any hormonal contraceptives or hormone replacement therapy within 3 months prior to Period I dosing.
- r. Volunteers who have ingested any vitamins or herbal products within 48 hours prior to Period I dosing.
- s. Volunteers who have any recent or significant change in dietary or exercise habits.
- t. Volunteers who have a history of difficulties swallowing, or any gastrointestinal disease which could affect the drug absorption.

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4. Study Check-in Procedures:

At each study check-in, the subjects will be briefly evaluated to assess if they continue to meet the study inclusion/exclusion criteria. In addition, a blood sample will be collected for a pregnancy screen (females only).

5. Study Exit Procedures:

- a. Study exit procedures will be completed within 14 days after the last blood sample collection. The exit procedures will include general observations, a physical examination, blood pressure, heart rate and temperature evaluation.
- b. The exit clinical laboratory procedures will include.
 - **HEMATOLOGY:** hematocrit, hemoglobin, WBC count with differential, RBC count, platelet count.
 - **CLINICAL CHEMISTRY:** serum creatinine, BUN, glucose, AST(GOT), ALT(GPT), albumin, total bilirubin, total protein, and alkaline phosphatase.
 - **URINALYSIS:** by dipstick; full microscopic examination if dipstick positive;
 - **SERUM PREGNANCY SCREEN (female subjects only)**

B. Study Design, Products and Procedures:

1. Study Design:

- a. Study Design: Single dose, two-way crossover, fasting
 - (1) Number of Study Periods: Two
 - (2) Confinement: Approximately 16 hours prior to and until at least 24 hours after dosing each period.

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- (3) Number of Subjects: Forty-eight healthy adult volunteers and no alternates will initiate the study.
- (4) Washout between Doses: At least 7 days.
- (5) Physical Activity: After dosing, subjects should remain in an upright position for four hours. (See also Appendix II)
- (6) Subject Safety and Monitoring: A sitting blood pressure and radial heart rate will be measured prior to dosing and at 12 hours after each dose. (See also Appendix V)

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2. Study Products, Randomization & Dosing:

a. Product and Randomization Code:

A= **Test Product** - 1 tablet of *test* product with 240 mL of room temperature water after an overnight fast (20 mg PRILOSEC® OTC Tablets distributed by Procter & Gamble)

B= **Reference Product** - 1 capsule of *reference* product with 240 mL of room temperature water after an overnight fast (20 mg PRILOSEC® Capsules manufactured for AstraZeneca LP by Merck & Co. Inc.)

b. Randomization Sequence:

Sequence 1 = A B
Sequence 2 = B A

c. Dosing: (See also Appendix III)

- (1) Dose = 1 capsule or tablet (1 x 20 mg capsule or tablet)
- (2) Doses per Subject: One dose in each of the two dosing periods (total of 2 doses per subject)
- (3) Dosing Schematic: Sequential dosing

3. Fluid and Food Intake:

- a. Fluid Intake: Subjects will consume 240 mL of room temperature water at 1 hour and 15 minutes prior to dosing. Water will not be allowed from 1 hour prior to dose administration until 1 hour after dosing, except that given with drug administration. (See also VI. Schematic and Appendix II)
- b. Fasting: A standardized meal will be served approximately 14 hours prior to dose administration after which a fast (except water) will be maintained until at least 4 hours after dosing. Clear fluids, such as water, will be allowed during fasting as described in (3.a.) Fluid Intake.
- c. Meals will be as scheduled. (See also VI. Schematic and Appendix II)

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4. Sampling Details:

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- a. Sample Volume & Collection Container: 1 x 7 mL of blood will be collected in heparinized vacutainers [Becton-Dickinson VACUTAINERS™ - green-top No. 7676].
- b. Sample Collection Schedule each Study Period: Within one hour prior to dosing (0 hour) and after dose administration at:

0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, and 16 hours
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- c. Samples per Subject: 25 blood samples per period x 2 study periods. (total of 50 samples, 350 mL total volume)
- d. Blood samples collected within 2 minutes of scheduled time will not be considered protocol deviations.
- e. Sample Collection and Processing: Samples will be collected by direct venipuncture, collection tubes will be inverted 5-10 times immediately after collection, placed in an ice bath, centrifuged at approximately 3000 RPM and 4°C for 10 minutes, return the samples to an ice bath, the plasma pipetted into duplicate amber polypropylene tubes, frozen at approximately -70°C ± 15°C and stored until shipment. Upon completion of the study, the "A" plasma samples will be shipped to the analytical facility for sample analysis. The duplicate "B" plasma samples will be shipped after confirmation of receipt of the "A" plasma samples. No shipment will occur without written consent from the Bioanalytical Laboratory Management at Mylan Pharmaceuticals.

C. Analytical Laboratory, Statistical Analysis and Final Report: (See also Appendix VI)

1. The analytical laboratory will measure the omeprazole plasma concentrations using a validated analytical method.
2. The statistical analysis will follow current recommendations and include the appropriate pharmacokinetic parameters and statistical analysis of the data.
3. The final report will include an overview of the clinical, analytical and statistical data collected over the course of the study.



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V. SCHEMATIC: Study Summary

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**A RELATIVE BIOAVAILABILITY STUDY COMPARING 20 MG PRILOSEC[®] OTC TABLETS
VERSUS 20 MG PRILOSEC[®] CAPSULES UNDER FASTING CONDITIONS**

	SCREENING	PERIOD I	PERIOD II	STUDY EXIT
Consent Document	X			
Medical History	X			
Physical Examination	X			X
Electrocardiogram	X			
Vital Signs	X	X	X	X
Laboratory:				
CBC with differential	X			X
Chemistry	X			X
HIV Antibody Screen	X			
Hepatitis B Screen	X			
Hepatitis C Screen	X			
Urinalysis	X			X
Urine Drug Screen	X			
Pregnancy Screen (females only)	X	X	X	X
Product Administered		X	X	
Blood Sample Collections for Drug Concentration (25 [0 to 16 hours])		X	X	

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VI. SCHEMATIC: Subject Flow Sheet by Period

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**A RELATIVE BIOAVAILABILITY STUDY COMPARING 20 MG PRILOSEC® OTC TABLETS
VERSUS 20 MG PRILOSEC® CAPSULES UNDER FASTING CONDITIONS**

STUDY DAY	TIME	DOSE	BLOOD SAMPLE NUMBER	BLOOD COLLECTION TIME	QUERY FOR ADVERSE EVENTS	VITAL SIGNS	FLUID INTAKE	MEALS
Day -1, 1600 (4:00) Report to Institute and Site Orientation								
	1800 (6:00)						480 mL	Dinner
Day 1	0645			Wake-Up			240 mL	
	0700		1	-1:00 to 0:00	X	X		
	0800	X	N.A.	0:00			240 mL	
	0815		2	0:15				
	0830		3	0:30				
	0900		4	1:00			240 mL	
	0920		5	1:20				
	0940		6	1:40				
	1000		7	2:00				
	1020		8	2:20				
	1040		9	2:40				
	1100		10	3:00				
	1120		11	3:20				
	1140		12	3:40				
	1200		13	4:00				
	1215						480 mL	Lunch
	1230		14	4:30				
	1300 (1:00)		15	5:00				
	1330 (1:30)		16	5:30				
	1400 (2:00)		17	6:00			240 mL	
	1500 (3:00)		18	7:00				
	1600 (4:00)		19	8:00			240 mL	
	1700 (5:00)		20	9:00				
	1800 (6:00)		21	10:00				
	1815 (6:15)						480 mL	Dinner
	1900 (7:00)		22	11:00				
	2000 (8:00)		23	12:00	X	X	240 mL	
	2200 (10:00)		24	14:00				
Day 2	0000 (12:00)		25	16:00				
	0800			** 24:00				

**May leave Institute 24 hours after dosing

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APPENDIX I

ADMINISTRATIVE STUDY RECORDS

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- A. **Subject Enrollment and Identification:** Participants will be consecutively and tentatively enrolled in the study, pending the outcome of screening procedures, in the sequence they are recruited and reviewed during screening. If participants are dropped for not meeting enrollment criteria, the first qualifying volunteer will replace them.

The participant's initials will be utilized as subject code.

When the participants are admitted to the study site, they will be properly identified and a pre-labeled wristband will be applied. The wristband will contain the following information: subject number, subject code, subject name and the study protocol number. During confinement, the non-removable wristband will identify subjects for any study-related activity. During the ambulatory portion of the study, a tactful query will confirm subject identity prior to blood sample collection or any study-related activity.

- B. **Study Charts and Source Documents:** A study chart will be maintained on site for each participant to file records such as general observations, medical history, medication history, physical examination, electrocardiograms, and clinical laboratory data source documents and related documentation. The origination record will be considered the data 'source document'.
- C. **Case Report Forms:** Case report forms (CRF) will organize and summarize all pertinent data for this study, e.g. medical and medication history, physical examinations, screening tests and related information. The CRF's will be available for inspection by the Sponsor's monitors and/or representatives before, during, or upon completion of the study. All hand written data must be in legible black ink. All corrections will be dated and initialed. One copy of the case report forms will be forwarded to the Sponsor with a clinical report summary. The clinical investigators will retain the originals unless otherwise specified in writing by the Sponsor.
- D. **Data Collection:** All clinical study data will be collected by the clinical investigator(s) and staff and recorded on source documents. The data will be directly recorded on or transcribed to study specific case report forms. The clinical investigator(s) will assume responsibility for ensuring the completeness and accuracy of all clinical documents.

The analytical investigator(s) and staff will collect all analytical data. A copy of the analytical data and an analytical report summary will be forwarded to the Sponsor. The analytical investigator(s) will assume responsibility for ensuring the completeness and accuracy of all analytical documents.

The statistical staff will assume responsibility for ensuring the completeness and accuracy of all statistical documents and documentation.

- E. **Retention and Availability of Investigational Records:** The clinical investigators will maintain drug records, CRF's, and signed subject consent documents until and unless instructed in writing by the Sponsor that records may be destroyed or forwarded to the Sponsor. In accordance with U.S. Federal Regulations, these records will be available for inspection and copying if requested by a properly authorized employee of the U.S. Food and Drug Administration.

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APPENDIX II

STUDY VOLUNTEER INSTRUCTIONS, ACTIVITY, & MEALS

COPYA. Volunteer Instructions:

1. Volunteers will be instructed to avoid nonprescription medications within 14 days of Period I dosing. Any nonprescription medication consumption reported will be reviewed by the investigators prior to dosing. At the discretion of the investigator(s), these volunteers may be enrolled if the medication is not anticipated to alter study integrity.
2. Volunteers will be instructed to report to the investigator(s) any prescription or nonprescription medication consumed over the course of the study. The investigator(s) will address the significance of the reported medication consumption on study integrity. At the discretion of the investigator(s), these volunteers may continue study participation if the medication is not anticipated to alter study integrity.
3. Volunteers will be instructed to abstain from consuming grapefruit products, caffeine and/or xanthine-containing products (i.e. coffee, tea, caffeine-containing sodas, colas, and chocolate etc.) at least 48 hours prior to days on which dosing is scheduled and during the periods when blood samples are collected. At the discretion of the investigator(s), volunteers who violate this instruction may be enrolled or allowed to continue study participation if the amount of product consumed is not anticipated to alter study integrity.
4. Volunteers will be instructed to abstain from consuming alcohol at least 48 hours prior to days on which dosing is scheduled and during the periods when blood samples are being collected. At the discretion of the investigator(s), volunteers who violate this instruction may be allowed to continue in the study if the timing and amount of alcohol consumed is not anticipated to alter study integrity.
5. Volunteers who have violated any of the above instructions may be excluded or dropped from the study at any time at the discretion of the investigator(s).

B. Physical Activity:

1. During confinement, only non-strenuous activity will be permitted. Following dose administration, subjects must remain in an upright or supine position or as per protocol to assure subject safety. If symptoms of dizziness or lightheadedness occur secondary to phlebotomy or investigational product, the subject will be encouraged to remain in a sitting or supine position until the symptoms have resolved.

C. Meals and Diet:

1. Type of Meals: Subjects will be served standardized meals and beverages. Meals will be the same in content and quantity during each confinement period.
2. Diet Restriction: No grapefruit, caffeine or xanthine-containing food or drink will be allowed during the confinement portions of the study. (See also A.3. above)
3. Fluid Restriction: Fluids will be restricted as described per protocol. During those confinement study hours when fluids are not restricted, they will be allowed ad lib. if requested, but will generally be controlled to avoid fluid overload and abuse.

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APPENDIX III
DRUG ACCOUNTABILITY

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- A. Product Shipment: The drug supplies for this study should be shipped to:
- PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104
- B. Product Receipt and Randomization: Upon receipt of drug supplies, the investigator or designee will conduct an inventory and record date received and the amount of drug shipped. If pertinent, the product will be randomized to dispensing inventory and retention inventory.
- The dosing product randomization code will be determined prior to study initiation by the investigator's statistical staff unless otherwise arranged by the sponsor. The randomization code will only be known by the statistical and inventory control staff. The randomization code will only be available for statistical analysis and preparation of the final report. Any other requests must be in writing and approved by the Sponsor.
- C. Product Blinding: The staff involved in monitoring the subjects, collecting subjective and objective data, and querying the subjects on adverse events will be blinded, as much as possible, to the product source under evaluation.
- D. Drug Dose Package Labeling: The drug's package label for the dose administration container should contain, at the minimum, the subject's study number, study period, date, investigator, study number and Sponsor name.
- E. Dose Administration: Immediately prior to dosing, each subject's identification wristband label and drug dispensing vial label will be checked to assure there is a subject number match between the two labels. All doses will be administered as intended by the protocol and as authorized by the medical investigator. Immediately after product administration, the subject's oral cavity will be checked to confirm complete medication and fluid consumption. Dose administration will be immediately recorded on the Master Flow Sheet.
- The investigator or designee will accurately record the date and amount of medication dispensed to each subject on the drug administration log. The inventory control staff or designee will record dose administration on the subjects case report form.
- F. Retain Samples: It is the responsibility of the Sponsor to ship a sufficient number of dosage units to allow the clinical research facility to maintain an appropriate sampling on site as per federal requirements. Drug supplies provided for this study will be stored in a locked room free of environmental extremes and with restricted access. Periodic drug supply inventories and storage facility inspections will be conducted during the study.
- G. At the conclusion of the study, the investigator or designee will prepare an overall summary of all drug supplies received and used for the Sponsor. The remaining dosage units will be retained in a secure environment for the appropriate period of time as per federal requirements.

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APPENDIX IV

COPY**BLOOD SAMPLE LABELING, PROCESSING, STORAGE & TRANSPORT**

- A. **Sample Labeling:** The labels for all biological sample collection and storage containers will contain the subject's number, dosing period, collection date, investigator, study number and sample number. It is recommended to also include sample source and study hour.
- B. **Collection of Blood Samples:** Unless otherwise directed in the protocol, blood samples will be sequentially collected via direct venipuncture at intervals as specified in the protocol. The actual time of sample collection will be recorded on the Master Flow Sheet.
- C. **Sample Processing:** The blood samples may remain at the blood acquisition station until all samples have been collected for that collection period. The samples should be transferred to the processing laboratory in a timely manner. The blood samples will be processed as per protocol and the matrix transferred to the polypropylene transport tube. Unless otherwise specified in the protocol or requested in writing by the Sponsor, the time between sample collection and freezer storage should not exceed 1.5 hours.
- D. **Sample Storage:** Upon completing sample processing, the samples should be immediately placed in a freezer and stored at the protocol specified temperature until transfer or shipment to the analytical laboratory.
- E. **Transfer or Shipment of Samples:** The clinical staff will inventory the samples which are to be transferred or shipped to the analytical laboratory. The Sample Inventory record will accompany the frozen plasma samples as per Standard Operating Procedures.

For sample transfer, the inventoried samples will be released to the custody of the analytical laboratory staff for audit, inventory control and storage. Notification of sample transfer will be communicated via FAX to the Sponsor.

For sample shipment, the samples will be packed in ample dry ice within a styrofoam container and shipped via overnight express delivery to the analytical facility. Notification of sample shipment will be communicated via FAX to the analytical facility and Sponsor. The samples will be tracked by administrative staff to assure arrival in a safe and timely manner.

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APPENDIX V

SUBJECT SAFETY MONITORING AND ADVERSE EVENTS

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- A. Subject Safety Monitoring: Study staff will monitor the subjects throughout the confinement portion of the study. Between study periods and during the ambulatory portion of the study, staff will be available during regular working hours and via an answering service for subject queries. The medical investigator or qualified medical designee will be on-site and/or available by pager throughout the study.

The Sponsor will designate qualified individuals to maintain a close liaison with the investigator(s) and study staff to ensure the clinical investigation follows the approved protocol and the research intent of Good Clinical Practice. Internal standard operating procedures for compliance with applicable government regulations will also be applied. This liaison will be documented by personal and/or telephone visits prior to study initiation and during the study to enable periodic reviews as well as clarify any questions which may arise during the study. During onsite visits, Sponsor study monitors will be provided access to all study source documents to ensure the integrity of the data.

- B. Adverse Events: The staff will record all adverse events observed, queried or spontaneously volunteered by the subjects. Unless otherwise required by the protocol, the adverse event query should occur prior to dosing, every 12 hours during confinement, and at each return study visit after dose administration. The elicited query will be as follows: "How do you feel? How have you felt since ____?" Subjects experiencing adverse events will be followed until the event has resolved to the satisfaction of the investigator(s). If the subject is terminated by the investigator(s), the Sponsor will be notified in writing within five working days.

Any adverse event, which is considered both serious and unexpected (as defined by the FDA), shall be reported to the Sponsor and IRB promptly by telephone and/or in writing within fifteen calendar days of discovery. Any unexpected fatal or life-threatening event shall be reported to the Sponsor and IRB promptly by telephone and in writing within seven calendar days.

Subjects withdrawn from the study due to any adverse event(s) will be followed until an outcome is determined. All adverse events, regardless of severity and whether or not ascribed to the test article, are to be recorded in the appropriate section of the case report form.

- C. Removal of Subjects from Study: Subjects will be advised they are free to withdraw from the study at any time. Over the course of the study, the investigator(s) may withdraw any subject from the study in the case of unnecessary risk, adverse drug events or noncompliance. When a subject withdraws from the study, all safety data normally required at the end of the study will be obtained, if possible.
- D. Termination of study: If, in the opinion of the investigators, the incidence and severity of adverse events outweighs the benefit of continuing the study, the investigators may terminate the study. In the event this course of action is to be pursued, the investigators will make every attempt to communicate with the Sponsor prior to the decision to develop a complete plan of action and to assess outcomes.

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APPENDIX VI

ANALYTICAL METHODOLOGY AND STATISTICAL ANALYSIS

COPYA. Analytical Procedures:

1. Samples from subjects who complete all periods of the study and who are not withdrawn by the clinic or the pharmacokineticist will be assayed for omeprazole by analysts blinded to the randomization scheme. Chromatographic procedures developed by CEDRA Corporation will be used.
2. Specific details of recovery, linearity, specificity and sensitivity of the assay will be included in the final report.

B. Data Analysis:

1. The bioequivalence of 20 mg PRILOSEC® OTC Tablets distributed by Procter & Gamble to 20 mg PRILOSEC® Capsules manufactured for AstraZeneca LP by Merck & Co. Inc. will be determined by a comparison of various pharmacokinetic parameters derived from the plasma concentration-time curves (e.g. AUC 0-tLDC, AUC 0-inf, Cpeak).
2. It is the sponsors intent to complete this study in one cohort. Should separate enrollments be required to complete the intended number of subjects all enrollments will be treated as one group for statistical analysis purposes under the following conditions: i) recruiting for additional enrollment(s) began before the end of the final period for the previous enrollment; ii) subjects are recruited from the same population, under the same protocol requirements; iii) dosing of additional enrollments began as soon as practical after their recruitment.

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APPENDIX VII

REGULATORY

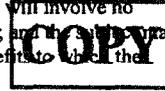
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- A. **Institutional Review Board:** The investigator(s) agree to provide the PRACS Institutional Review Board (IRB) with all appropriate material, including a copy of the protocol, consent document and advertising text (if study specific advertising is used). The study will not be initiated without written IRB approval of the research plan and consent document. Copies of the IRB approval should be forwarded to the Sponsor. The investigator(s) will provide appropriate reports on the progress of this study to the IRB and Sponsor in accordance with applicable government and/or Institute regulations and in agreement with Sponsor policy. The IRB will be informed of any modifications of the protocol or consent document. Approval, in writing, will be obtained from the IRB prior to implementation of any changes which may increase subject risk or which may alter the validity or objectives of the data collected. A copy of the IRB approval letter covering such alterations will be furnished by the investigator(s) to the Sponsor. For modifications to the protocol which are administrative in nature, or do not affect subject risk, the IRB will be notified in writing by the investigator(s), with a copy to the Sponsor.
- B. **Consent Document:** A properly executed, written consent in compliance with current U.S. federal code shall be obtained from each subject prior to entering the trial or prior to performing any unusual or non-routine procedure involving risk to the subject. A copy of the consent document(s) to be used will be reviewed and approved by the Sponsor. It will be submitted by the investigators to the PRACS IRB for review and written approval prior to the start of the study. The investigator(s) shall provide a copy of the consent to the subject and a signed copy shall also be maintained in the study records. Attention is directed to the basic elements required in the consent document under U.S. Federal Regulations for Protection of Human Subjects:
1. A statement verifying the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental.
 2. A description of any reasonably foreseeable risks or discomforts to the subject.
 3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
 4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
 5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility the U.S. Food and Drug Administration and the study Sponsor may inspect the records.
 6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
 7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury to the subject.

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8. A statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.



Additional elements of consent, if appropriate, must be provided to the subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject which may result from participation in the study.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

C. **Investigator's Statement:** The investigator agrees to conduct the trial as outlined in the approved protocol and in accordance with the Sponsor's guidelines and all applicable U.S. federal government regulations. These Good Clinical Practice guidelines include, but are not limited to:

1. Permission to allow the Sponsor, the U.S. FDA or other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner which ensures subject confidentiality. If this study is to be inspected by a regulatory agency, the Sponsor will be notified as soon as possible.
2. Submission of the proposed clinical investigation, including the protocol, consent document, and advertising text (if study specific advertising is used) to a duly constituted IRB for approval and acquisition of written approval for each, prior to study initiation.
3. Use of a written consent document obtained prior to entry into the study or prior to the performance of any non-routine procedures that involve subject risk. The consent document(s) must contain all the elements as specified in the U.S. Federal Regulations and which has been previously approved by the Sponsor and the IRB.
4. Submission of any proposed change in or deviation from the protocol to the IRB, using a signed formal amendment document prepared by the Sponsor and/or investigator. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, IRB approval must be obtained prior to implementation. For changes that do not involve risk or affect the validity of the investigation or the subject's rights, prior IRB approval may be obtained by expedited review.
5. Documentation and explanation of protocol deviations will be made on the appropriate case report form page or by written documentation to the Sponsor.

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6. The investigator shall promptly report to the Sponsor any severe adverse event that may reasonably be regarded as caused by, or probably caused by, the test article.
7. The investigator shall submit timely progress reports to the IRB and Sponsor at appropriate intervals, but not to exceed 1 year. The final report should be submitted to the IRB within 4 months after study completion, termination or discontinuation.
8. The investigator and study staff shall maintain accurate source documents from which case report form data are based and accountability records which show the receipt and disposition of all test article(s) shipped to the investigator by the Sponsor.

The investigator agrees all information provided by the Sponsor, including pre-clinical data, protocols, case report forms, verbal and written information, will be kept strictly confidential and confined to the personnel involved in conducting the trial. It is recognized this information may be given in confidence to the PRACS Institutional Review Board.