

Appendices

1

Appendix 1
Study Protocol

**ADVANCED CARE PRODUCTS
PERSONAL PRODUCTS CORPORATION
Skillman, New Jersey**

DRUG CLINICAL PROTOCOL

**"Evaluation of the Efficacy of Phenazopyridine Hydrochloride
(Formula PD-F-0016) as a Urinary Analgesic in Women with Urinary Tract
Infections"**

**Protocol Number 99-001-P
August 20, 1999**

**Advanced Care Products
Personal Products Corporation
Division of McNeil-PPC Inc.
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PROTOCOL SUMMARY
Protocol 99-001-P

1. **Objective:** To determine the efficacy of phenazopyridine hydrochloride as a short term urinary analgesic in women as compared to placebo.
2. **Phase:** IV
3. **Design:** Double blind and placebo controlled.
4. **Number of Subjects:** 80 subjects randomized to 2 groups
5. **Type of Subject:** Subjects with pain due to a urinary infection as described by the protocol.
6. **Key Inclusion/Exclusion Criteria:**
 - Healthy female, 12 years or older, non-pregnant and non-nursing
 - No history of renal or hepatic dysfunction
7. **Test Drug Dosage:** One single oral dose of Phenazopyridine hydrochloride (oral dose consists of 2 tablets containing 95mg of medication per tablet).
8. **Placebo:** Inactive ingredients tablets. One single oral dose consisting of 2 tablets.
9. **Efficacy Parameters:** Efficacy assessments will include relief of symptoms of general discomfort, dysuria, frequency to void and urine volume. Overall assessment of the study medication will be also assessed.
10. **Safety Parameters:** Adverse experiences.
11. **Data Analysis:** Efficacy assessments will include the overall assessment of therapy, time to complete relief of general discomfort (using a stopwatch technique), average volume per void, number of voids per subject and drug effect duration.
12. **Risk/Benefit Summary:** Minimal risk to subject. Subjects randomized to placebo may not experience relief of symptoms during participation in the study. Possible benefit may be temporary relief of urinary symptomatology if randomized to active group.

TIME AND EVENTS SCHEDULE PROTOCOL No. 99-001-P

| Procedure | Day 1 Admission Visit | Day 1 Admission Visit | Follow-Up Contact |
|--|-----------------------|---|-------------------|
| Time | 0 | Six-hour post-dosing observation period | Day (1-3) |
| Informed Consent Signed/Inclusion Exclusion Criteria | X | | |
| Baseline Symptoms Assessment and Void Sample | X | | |
| Brief Medical History and Physical Examination | X | | |
| Symptoms Assessment | X | | |
| Sample Pregnancy test/Urine Dip Stick | X | | |
| Administer Study Medication | X | | |
| Record Efficacy Assessments | | X | |
| Overall Assessment of Study Medication | | X | |
| Record Adverse Event | | X | X |
| Concurrent Medications Reviewed for Eligibility at Admission Visit | X | | |
| Follow Up with Subject | | | X |
| Complete Case Reports Pages | X | | X |

TABLE OF CONTENTS

| | | |
|-----|---|----|
| 1.0 | <u>INTRODUCTION</u> | 1 |
| 1.1 | <u>OBJECTIVE</u> | 4 |
| 1.2 | <u>DESCRIPTION OF STUDY</u> | 4 |
| 1.3 | <u>SUBJECT SELECTION</u> | 6 |
| | 1.3.1 Study Population | 6 |
| | 1.3.2 Inclusion Criteria | 6 |
| | 1.3.3 Exclusion Criteria | 7 |
| 1.4 | <u>PROCEDURES</u> | 8 |
| | 1.4.1 Research Plan | 8 |
| 1.5 | <u>MATERIALS, SUPPLIES AND LABELS</u> | 11 |
| | 1.5.1 Test Articles | 11 |
| | 1.5.2 Supplies | 12 |
| | 1.5.3 Labeling | 12 |
| | 1.5.4 Packaging | 12 |
| 1.6 | <u>MANAGEMENT OF INTERCURRENT EVENTS</u> | 13 |
| | 1.6.1 Recording Adverse Experiences | 13 |
| | 1.6.2 Departure from the Protocol | 15 |
| | 1.6.3 Concurrent Medication | 16 |
| | 1.6.4 Modifications of the Protocol | 16 |
| 1.7 | <u>REPORTING REQUIREMENTS</u> | 16 |
| 1.8 | <u>ACCEPTABILITY OF CASE REPORT FORMS</u> | 17 |
| 1.9 | <u>MONITORING/ON-SITE AUDITS</u> | 18 |
| 2.0 | <u>SAMPLE SIZE</u> | 18 |
| 2.1 | <u>STATISTICAL PROCEDURES</u> | 19 |
| | 2.1.1 Efficacy: Primary and Second Measures | 19 |
| | 2.1.2 Safety | 20 |

TABLE OF CONTENTS
(CONTINUED)

| | | |
|-----|---|----|
| 2.2 | <u>USE OF INFORMATION AND PUBLICATION</u> | 20 |
| 2.3 | <u>DISPOSITION OF STUDY MATERIALS</u> | 20 |
| 2.4 | <u>COMPLETION OF STUDY</u> | 21 |
| 2.5 | <u>RECORDS RETENTION</u> | 21 |
| 2.6 | <u>INVESTIGATOR AGREEMENT</u> | 22 |
| 2.7 | <u>ATTACHMENTS</u> | 23 |

Protocol No. 99-001-P

August 20, 1999

1.0

INTRODUCTION

Phenazopyridine hydrochloride, an azo dye, is the active ingredient in over the counter medications for symptomatic relief of urinary tract infections (UTIs). It has widely been used in the United States as a urinary tract analgesic since 1914. It is still used for its local analgesic action on mucous membranes of the urinary tract. Phenazopyridine hydrochloride is excreted in the urine where it exerts a topical analgesic action on the urinary tract mucosa. The precise mechanism of action is not known. However, the underlying cause of irritation must be determined and treated (i.e. antibacterial therapy for infection). Phenazopyridine hydrochloride tablets have been available over the counter since the 1960's. Currently, phenazopyridine hydrochloride products with doses of approximately 100 or 200 mg per tablet, are available on prescription for use as a urinary tract analgesic. Doses less than 100 mg are available OTC.

Phenazopyridine hydrochloride is a commercially available over the counter (OTC) urinary pain relief medication distributed by *Advanced Care Products, Personal Products Company* as URISTAT® (95 mg per tablet). URISTAT® is indicated for short-term use to relieve symptoms such as pain, burning, and urinary urgency and/or frequency caused by irritation of the lower urinary tract mucosa. The recommended dosage of URISTAT®, 2 tablets (95 mg per tablet), 3 times per day for a total of 6 tablets per day, not to exceed 12 tablets over a 2 day period, is safe to use as a urinary tract analgesic. URISTAT® should not be administered to individuals with renal insufficiency and should be kept out of the reach of children.

1.0.1 **Preclinical Data**

Phenazopyridine hydrochloride has a low order of toxicity as shown by the following LD₅₀ values:

| <u>Species</u> | <u>Route</u> | <u>LD₅₀</u> |
|----------------|--------------|------------------------|
| Rat | oral | 472 mg/kg |
| Rat | i.p. | 200 mg/kg |
| Mouse | i.p. | 180 mg/kg |

The amount of phenazopyridine hydrochloride delivered to an average individual in a 6 tablet daily dose is 11.64 mg/kg or 3.88 mg/kg at each 2 tablet interval. These values are far below the reported LD₅₀ values.

Protocol No. 99-001-P

August 20, 1999

Ten mongrel dogs were given daily oral doses of phenazopyridine hydrochloride at the rate of 60 mg/day for an unspecified number of days (Slatter and Davis, 1974). The dogs were euthanized at intervals of 24 hours, starting at 24 hours after the first dose. The lachrymal glands were removed and examined for histopathological changes. It is suggested that phenazopyridine hydrochloride or its metabolite decreases the synthesis of secretory granules. After incorporation of the compound in to the granules, they undergo fusion and subsequent degeneration (Slatter and Davis, 1974). Reproduction studies have been performed in rats at doses up to 50 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus.

Long term administration (2 years) of 225 grams/kg of phenazopyridine hydrochloride has induced neoplasia in the large intestine of rats (IARC, 1979). Life time administration of 81 g/kg of phenazopyridine hydrochloride has induced neoplasia in the liver of mice (IARC, 1979).

1.0.2 Clinical Data

The metabolism and urinary excretion of phenazopyridine hydrochloride has been studied in humans. The bio-transformation is hepatic and the elimination is renal. In six subjects, 90% of a 600 mg dose was eliminated in the urine in 24 hours as unchanged drug and metabolites (6.9% appeared as aniline, 18% as 4-acetoaminophenol and, 41% as phenazopyridine hydrochloride and o-aminophenol in trace amounts). More than 50 percent of the administered dose was reductively cleaved to yield aniline and triaminopyridine, suggesting that the metabolites of aniline probably contribute to the reputed analgesic effect of phenazopyridine hydrochloride on the urinary tract mucosa (Johnson and Chartrand, 1976).

Several clinical trials have been conducted. In 1943, one trial administered 200 mg phenazopyridine hydrochloride, 3 times per day for 2 weeks to 118 subjects with urinary infections and in 1970, 49 subjects with urinary infections were administered 200 mg phenazopyridine hydrochloride 3 times in 1 day. No adverse effects were observed during the studies. In 1975, clinical trials were conducted on approximately 200 subjects with urinary tract infections. They were administered phenazopyridine hydrochloride 3 times a day for 5 days. The documented adverse effect was 13% of the subjects experienced gastrointestinal intolerance (Zelenitsky and Khanel, 1996).

Protocol No. 99-001-P

August 20, 1999

Phenazopyridine hydrochloride should not be administered to individuals with renal insufficiency. In these subjects, transient acute renal failure may occur. It is recognized that the rate of renal excretion of phenazopyridine from the body is influenced by the level of renal function. A dose of 200 mg of phenazopyridine hydrochloride given orally to normal subjects was excreted in an average of 20 hours with peak excretion occurring in the second and third hour after ingestion. In contrast, in 10 subjects with urologic disorders, 3 of whom were azotemic, excretion was delayed to an average of 27 hours. Although the mechanisms of renal excretion of the dye have not been thoroughly studied, it has been suggested that the drug toxicity in the collecting tubule results from concentration of the drug or a toxic metabolite in the tubules or papillary interstitial tissue (Alano and Webster, 1970). In overdose quantities, phenazopyridine hydrochloride has been known to produce methemoglobinemia. Also, hemolytic anemia, hepatotoxicity and nephrotoxicity have been attributed to an overdose. The toxic effects of phenazopyridine hydrochloride are attributed to its metabolite, 2,3,6-triaminopyridine, which has been shown to auto-oxidize at neutral pH, generating superoxide radical and hydrogen peroxide (Munday and Fowke, 1994). The first reported instance of methemoglobinemia due to ingestion of phenazopyridine hydrochloride was in 1951. In the 1960's, several cases of acquired methemoglobinemia and Heinz body hemolytic anemia associated with therapeutic dosage of phenazopyridine hydrochloride were reported in subjects with renal insufficiency (Cohen and Bovasso, 1971). Adverse effects including methemoglobinemia, hemolytic anemia, and acute renal failure have been rarely described. Since the risk of toxicity is increased with prolonged therapy and acute and chronic overdose, it is recommended that phenazopyridine therapy be limited to 2 days and avoided in subjects with impaired renal function (Zelenitsky and Zhanel, 1996).

There are reported cases of accidental ingestion of phenazopyridine hydrochloride by children, ages 13 to 18 months (Wander et al. 1965; Bloch and Porter, 1969; Cohen and Bavasso, 1971). All cases resulted in methemoglobinemia after ingestion of 700 to 8000 mg of phenazopyridine hydrochloride at one time. The children received medical treatment within 2 hours and fully recovered. Phenazopyridine hydrochloride is reported to be toxic to children at oral doses ranging from 35 to 400 mg/kg.

Protocol No. 99-001-P**August 20, 1999****1.1****OBJECTIVE**

This study will evaluate the efficacy and safety of phenazopyridine hydrochloride (Formula PD-F-0016) as a short term treatment of urinary symptoms associated with urinary tract infections in women.

1.2**DESCRIPTION OF STUDY**

This is a randomized, double-blind, parallel-group, placebo-controlled, single dose analgesic evaluation of the efficacy and safety of phenazopyridine hydrochloride as a short term treatment of urinary symptoms associated with urinary tract infections in women. The study will be conducted in approximately three study centers. Approximately 80 subjects will be enrolled, 40 subjects per treatment group. Phenazopyridine hydrochloride will be orally administered once as two tablets. A placebo control will be used to establish the magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

All subjects will be seen and evaluated by the investigator during the baseline admission visit. Once the eligibility criteria are met, the subject signs the informed consent, the study procedures are explained to her and she is randomized, the investigator or authorized designee will work closely with the subject to collect all efficacy parameters, including the collection of urine samples during the first six hours post-dosing. The subject will be asked to void her bladder before taking the study medication. Subsequent voids and volume collected will be assessed during the entire first six-hour post-dosing observation period. Therefore, subjects are required to remain at the study facility during this time period. Additional information including their overall clinical progress will be also monitored. The subject should report promptly to the investigator or authorized designee any unusual or adverse experience (incidence and severity) during the first six hours post-dosing period.

There will be a follow up contact (day 1-3 post-dosing) in which the investigator or authorized designee will review with the subject whether her UTI condition has resolved. The incidence and severity of any adverse experience that may have occurred since the completion of the six-hour post-dosing observation period and the administration of the medication to treat her UTI condition will also be assessed.

Protocol No. 99-001-P

August 20, 1999

Each subject will be randomly assigned to receive either one oral dose of 2 tablets (95mg each) of phenazopyridine hydrochloride or one oral dose of 2 tablets of placebo. All study medication will be administered at the clinical site and monitored for 6 consecutive hours.

Subjects will only be entered into the study, if on the day of study dosing, they meet a baseline pain level on the Visual Analog Scale (VAS) of at least:

- Three for general discomfort
- Two for urgency to void and
- Two for dysuria (pain at urination)

Additionally, the combined sum of baseline pain level must reach at least seven on the VAS (See Attachment 1).

After the entire six-hour post-dosing observation period is complete, the subject will begin the medical treatment prescribed by the investigator to treat the urinary infection.

If supplemental analgesic medication is required at anytime during the first six-hour post-dosing observation period; the reason it is required, the pain intensity (from the VAS) at the time it is required and the name of the medication will be recorded in the source document, and the study subject will discontinue her participation in the study. The subject will be encouraged (but not required) to wait at least four hours post-dosing before taking supplemental pain medication, if there is no analgesic response to the study medication. The subject will be encouraged (but not required) to wait until the pain level has returned to the baseline assessment before taking supplemental pain medication. A final assessment of current pain and relief from starting pain will be made and recorded prior to a subject's taking supplemental analgesic medication. At the end of the six-hour observation period or at the time of taking supplemental analgesic medication whichever occurs first, the subject will make an overall assessment of the improvement of her symptoms by the study medication, selected from the following scale: excellent, very good, good, fair, poor (for more details see the Time and Events Schedule Flow Sheet, page ii).

Protocol No. 99-001-P

August 20, 1999

1.3. SUBJECT SELECTION**1.3.1 Study Population**

Approximately 80 females exhibiting a symptomatic uncomplicated urinary tract infection confirmed by urine dip stick and pain baseline symptoms with a VAS score on the day of study dosing of at least:

- Three for general discomfort
- Two for urgency to void and
- Two for dysuria (pain at urination)

will be entered into the study. Additionally, the combined sum of baseline pain level must reach at least seven on the VAS (See Attachment 1).

Prior to any study related procedures, the subjects must sign an informed consent form explaining the experimental procedures. Subjects must meet all the inclusion criteria and exhibit none of the exclusion criteria to be eligible for enrollment into the study. Exceptions to these inclusion/exclusion criteria may be allowed if pre-approved by the medical monitor. Any exceptions to the protocol must be documented on the case report form and source document(s) as described in Section 1.6.2 of this protocol.

1.3.2 Inclusion Criteria

Those subjects who meet the following criteria will be eligible for participation in this study:

- 12 years of age or older (Minors require parental or guardian consent)
- Females who are non-pregnant and non-nursing. A negative pregnancy test must be obtained on the day of study dosing on all women of child-bearing potential, including those who have had tubal ligations.
- Reporting or exhibiting on the day of study dosing on the Visual Analog Scale (VAS) a baseline pain level of at least:
 - Three for general discomfort
 - Two for urgency to void and
 - Two for dysuria (pain at urination)

Protocol No. 99-001-P**August 20, 1999**

Additionally, the combined sum of baseline pain level must reach at least seven on the Visual Analog Scale (VAS). General discomfort is defined as an overall assessment of the subject's symptomatology, which may include pain in the lower abdominal section. Dysuria is defined as pain during urination. Urgency to void is defined as an urgent need to urinate, even when urine flow is minimal.

- Confirmatory diagnosis of a symptomatic uncomplicated UTI by Urine Dip Stick.
- Ability to perform study procedures and supply the necessary information to the study personnel as required by the protocol.
- Otherwise in general good health, in the opinion of the investigator.
- Has signed the informed consent form agreeing to participate after the study has been fully explained.

1.3.3 Exclusion Criteria

Subjects with any of the following criteria will be excluded from this study:

- Prior use and knowledge of phenazopyridine hydrochloride and its effects in urine discoloration.
- Use of any systemic anti-infective within seven days of admission.
- Use of any over the counter or prescription analgesic (Tylenol®, Motrin®, etc.) within 24 hours of the day of study dosing.
- History of sensitivity to phenazopyridine hydrochloride.
- Current history of renal dysfunction.
- Current history of hepatic dysfunction.
- Current history of diabetes.
- Has had more than two documented Urinary Tract Infections within a 12-month period or subjects with UTIs that do not clear up with proper treatment .
- At risk in terms of the precautions, warnings, and contraindications in the package insert for phenazopyridine hydrochloride.
- Employees of Johnson & Johnson, its affiliates, or employees of the clinical investigational site.
- A history of drug abuse or alcohol abuse within 6 months.
- Current participation in a clinical trial or received an experimental drug or used an experimental device in the last 30 days prior to admission into this study.

Protocol No. 99-001-P**August 20, 1999**

1.4 PROCEDURES

Every subject interested in participating will be completely informed of the study requirements and procedures including the risks. Prior to entry into the study, all subjects are required to read and sign an informed consent form.

1.4.1 Research Plan**Admission**

Each subject will be assessed for study eligibility prior to study entry. The investigator or designee will obtain a brief medical history, perform a physical examination and complete all procedures listed in the time and events schedule flow sheet (page ii). Subject eligibility will be determined by the inclusion and exclusion criteria.

Subject's Evaluation

The subject reports general discomfort, dysuria and urgency to void associated with a urinary tract infection. The investigator will assess with the subject that her symptoms on the day of study dosing are at least:

- Three for general discomfort
- Two for urgency to void and
- Two for dysuria (pain at urination)

on the Visual Analog Scale (VAS)

Additionally, the combined sum of baseline pain level must reach at least seven on the VAS. This information will be recorded by the investigator in the subject's source documentation chart and case report form. Symptoms reported by the subject or findings noted during the physical examination will be also recorded.

Laboratory tests to be performed:

- a) Urine dip stick (confirmatory diagnosis for urinary tract infection)
- b) FACT PLUS® test for pregnancy or pregnancy test of equal or greater sensitivity (if applicable)

After determining the subject's eligibility and interest in study participation, the investigator or designee will explain the study and study procedures in detail. Once all admission procedures are completed, subjects will be assigned drug according to a

Protocol No. 99-001-P**August 20, 1999**

randomization schedule (provided by Advanced Care Products). Randomization will be stratified to ensure an equal distribution of subjects to each arm of the study. Study medication must be dispensed in sequential numerical order, starting with the lowest number first.

Study Medication Use and Procedures

The study medication will be administered during the baseline admission visit by the investigator or authorized designee. Qualified subjects will be randomized in equal numbers to:

- A single dose of 2 tablets (95mg) of phenazopyridine hydrochloride or
- A single dose of 2 tablets of matching placebo

The subject will be asked to void immediately before the administration of study medication (dosing). Study medication will be swallowed with eight (8) ounces of water. Subsequently, the subject will evaluate her general discomfort relief. Assisted with a stop watch or equivalent device the subject will measure time to complete relief (no more general discomfort).

Simultaneously, following the administration of study medication, the number of voids and dysuria (pain at urination) assessments will be collected. At each void, relief of symptoms from starting baseline dysuria pain will be evaluated on a five-point scale consisting of: complete, a lot, some, a little, and none. Urine volume will be also collected at each void.

The subject should remain at the study facility for the first 6 hours post-dosing. The subject will be allowed to eat and drink "ad lib" but should remain at the study site. During this observation period, the subject will provide the study personnel with all the required observations, which will be entered in the subject's source documentation chart and case report forms. At the end of the six-hour observation period, the subject will make an overall assessment of therapy, selected from the following scale: excellent, very good, good, fair, poor (See Time and Events Schedule Flow Sheet).

If supplemental analgesic medication is required, during the first six-hour post-dosing observation period; the reason it is required, the pain intensity (from the VAS) at the time it is required and the name of the medication will be recorded in the source document, and the study subject will discontinue her participation in the

Protocol No. 99-001-P**August 20, 1999**

study. The subject will be encouraged (but not required) to wait at least four hours post-dosing before taking supplemental pain medication, if there is no analgesic response to the study medication. The subject will be encouraged (but not required) to wait until the pain level has returned to the baseline assessment before taking supplemental pain medication. A final assessment of symptoms from baseline will be made and recorded prior to a subject's taking the supplemental analgesic medication. At the end of the six-hour observation period or at the time of taking supplemental analgesic medication, whichever occurs first, the subject will make an overall assessment of therapy, selected from the scale: excellent, very good, good, fair, poor (See Time and Events Schedule Flow Sheet).

Each subject will be instructed to complete all information at the required times, as specified by the protocol. The completed information will be collected during the post-dosing six-hour observation period. An authorized designee will review and confirm the information with the subject and resolve any discrepancies before the subject leaves the study site. Baseline and subsequent measurements of general discomfort, urgency to void (number of voids and volume) and dysuria will be assessed.

The investigator or authorized designee will ask the subject for any complaints and adverse or unusual experiences that will be noted at this time in the subject's chart.

If any procedures such as dental work, where prophylactic antibiotic was used within 7 days prior to day of study dosing, subjects should refrain from enrolling as described in Section 1.3.2. and 1.3.3.

Follow up - Day 1-3

The subject must be contacted within 3 days post-dosing to determine if her UTI condition has resolved. The incidence and severity of any adverse experience that may have occurred since the completion of the six-hour post-dosing observation period and the administration of the medication to treat her UTI condition will also be assessed.

If a subject can not be reached for the follow up contact, a registered letter with return receipt will be sent requesting the follow up information.

Protocol No. 99-001-P

August 20, 1999

Discontinuation From the Study

Subjects will be discontinued from the study for the following reasons:

1. Adverse experience(s)
2. Subject choice
3. Supplemental medication taken
4. No follow-up contact possible

Discontinuation

The following discontinuation procedures are to be performed upon completion of the study or study discontinuation:

1. Collect all efficacy and safety information
2. Complete discontinuation/completion form

Study procedures for each visit are outlined on the Time and Events Schedule Flow Sheet.

1.5 MATERIALS, SUPPLIES AND LABELS**1.5.1 Test Articles**

The test product is phenazopyridine hydrochloride (Formula No.: PD-F-0016), a 2,6-diamino-3-(phenyazo) pyridine monohydrochloride. This Azo dye has a molecular weight of 249.70 and it is a light or dark red to dark violet, odorless, slightly bitter, crystalline powder with an empirical formula of $C_{11}H_{11}N_5 \cdot HCl$. The single dose of two coated tablets of study medication contains approximately 53% W/W of Phenazopyridine Hydrochloride, USP. Other ingredients present in the formulation are Lactose Hydrous, NF; Sodium Starch Glycolate, NF; Corn Starch, NF; Hydrogenated Vegetable Oil (Sterotex K); Colloidal Silicon Dioxide, NF and magnesium Stearate, NF. The two study medication tablets have a dark brown color and will be blister-packed inside a white study medication box.

The placebo control in this clinical study, is a single dose of two coated tablets containing no active ingredient (Formula No.: PD-F-1797) and identical in size and physical appearance to the active study medication. They will be blister packed inside a white study medication box.

All study medication should be stored at room temperature and out of the reach of children.

Protocol No. 99-001-P

August 20, 1999

1.5.2 Supplies

Advanced Care Products will provide the investigator with the following supplies:

1. Case Report Forms (CRFs)
2. Drug Inventory Sheets
3. Clinical Test Articles
4. Subjects Instructions
5. Stopwatch(s) or equivalent device(s)
6. FACT PLUS® Test for Pregnancy or equivalent

1.5.3 Labeling

A two-part tear-off blinded label containing the following information will be used:

- Dosage form and quantity
- Protocol number
- Active ingredients
- Route of administration
- Storage instructions
- Directions for use (see subject instruction sheet)
- Caution statement as required
- Keep out of reach of children
- Subject number
- Space for subject initials
- Name and address of sponsor

The tear-off portion of the label is to be removed at the time the study drug is dispensed and attached to the label accountability page of the case report form.

Identity of the drug, quantity and lot numbers will be concealed in a blinded area of the label (the investigator will be blinded throughout the study). This may be unblinded for emergency purposes only by rubbing off the silver-coated area. Any labels that have been unblinded should be reported to ACP and recorded appropriately in the case report form.

1.5.4 Packaging

All medication boxes will be standard white cartons with an outside two-part tear-off label. All packages will be closed with tamper evident seals. The two treatment groups are indicated below:

- Two dark brown coated tablets containing phenazopyridine hydrochloride (95 mg) (Formula No.: PD-F-0016) blister-packed with instruction for use.

Protocol No. 99-001-P**August 20, 1999**

- Two dark brown coated tablets containing no active ingredient (placebo)(Formula No.: PD-F-1797) blister-packed with instructions for use.

1.6**MANAGEMENT OF INTERCURRENT EVENTS****1.6.1 Recording Adverse Experiences**

After the administration of study medication (study dosing), all new adverse experiences which were not present at baseline (prior to study dosing) must be recorded. Any medical condition present at baseline, which remains unchanged or improves, should not be recorded as an adverse experience at the end of the study. However, if there is deterioration of a medical condition that was present at baseline (prior to study dosing), then this should also be considered a new adverse experience and recorded on the case report form. This information is obtained by questioning and/or examining the subject during the six-hour post-dosing period or during the follow up contact.

Study drug relationship for each adverse experience should be determined by the investigator using the following explanations:

Not related

- The experience is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitantly administered drugs.

Unlikely

- The experience was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitantly administered drugs.
- and does not follow a known response pattern to the test drug.

Possible

- The experience follows a reasonable temporal sequence from the time of drug administration,
- and/or follows a known response pattern to the test drug,
- but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitantly administered drugs.

Protocol No. 99-001-P

August 20, 1999

Probable

- The experience follows a reasonable temporal sequence from the time of drug administration,
- and follows a known response pattern to the test drug,
- and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitantly administered drugs.

Highly Probable

- The experience follows a reasonable temporal sequence from the time of drug administration
- and follows a known response pattern to the test drug,
- and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitantly administered drugs,
- and either occurs immediately following test drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

The term study drug includes the drug under evaluation and the active control drug.

Assessment of Severity

Severity of an adverse experience is defined as a qualitative assessment of the degree of intensity of an adverse experience as determined by the investigator or reported to him/her by subject. The assessment of severity is made irrespective of drug relationship or seriousness of the experience and should be evaluated according to the following scale:

1=Mild**2=Moderate****3=Severe**

A SERIOUS ADVERSE EVENT is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize

Protocol No. 99-001-P

August 20, 1999

the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

"Life-threatening" means that the consumer is at immediate risk of death from the event. It does not include an experience that, had it occurred in a more serious form, might have caused death. It also includes one which requires intervention to prevent it from becoming life-threatening.

"Hospitalization-Initial or Prolonged" is defined as a hospital admission or extension of hospitalization due to an adverse event.

"Disability" is defined as substantial disruption of a person's ability to conduct normal life functions.

1.6.2 Departure from the Protocol

A departure from this protocol will occur for an individual subject only in the event of an emergency which warrants such a departure. This departure is only for that subject. The investigator in attendance in such an emergency will contact immediately by telephone one of the *ADVANCED CARE PRODUCTS* personnel listed in this section of this protocol. The comments section of the case record form for that subject must describe the departure from the protocol and state the justification.

All serious adverse experiences, *the ADVANCED CARE PRODUCTS* medical monitor will be notified immediately by telephone (see page 16) and subsequently in writing within five (5) days of the occurrence. The experience must be described on the subject's case record form and source document. All adverse experiences are to be followed to satisfactory resolution and any measures taken as well as the follow-up results reported on the appropriate case report form and source document.

Unexpected adverse experiences which are associated with the use of the test article(s) must be **immediately reported** in writing to the Food and Drug Administration by the sponsor and to the Institutional Review Board by the investigator. The study monitors and the medical monitor are:

Protocol No. 99-001-P

August 20, 1999

Frederick L. Cone
Manager, Clinical Research
Advanced Care Products
Personal Products Company
691 US #1 - P.O. Box 6024
North Brunswick, New Jersey 08902-0724
Office: (732) 524-1436
E mail: Fcone@cpcus.jnj.com

David H. Upmalis, M.D.
Executive Director, Clinical Affairs
Advanced Care Products
Personal Products Company
691 US #1 - P.O. Box 6024
North Brunswick, New Jersey 08902-0724
Office: (732) 524-1426
E mail: Dupmali@cpcus.jnj.com

If none of the above are available, call (908) 524-0400
(Johnson & Johnson operator after hours).

1.6.3 Concurrent Medication

Other medications may be used during the duration of the study. The use of any medication other than study medication will be reported on the source document. Use of any type of analgesic or pain reliever during the first six-hour post dosing will discontinue the patient for continuing her participation. The investigator should notify the ACP monitor, when any deviation or protocol violation of this nature should occur.

1.6.4 Modifications of the Protocol

Neither the investigators nor the Advanced Care Products monitor will modify this protocol without first obtaining the concurrence of the other. The party initiating a modification will confirm it in writing.

1.7 REPORTING REQUIREMENTS

All reports and communications relating to subjects in the study will identify each subject with the subject's initials and by the subject's study number only.

Protocol No. 99-001-P**August 20, 1999**

1.7.1 Regulatory Documentation**Documents that must be submitted to Advanced Care Products
(Items 1-7 Prior to Initiation of the Study):**

1. Signed and Completed FDA Form 1572.
2. Assurance that an IRB that complies with the requirements set forth in Title 21 Part 56 of the Code of Federal Regulations will be responsible for approval of the clinical study. The required documentation will consist of the name and address of the IRB and a current list of IRB members, including the name, title, sex, occupation, and any institutional affiliation of each member. If accompanied by a letter of explanation from the IRB, a general assurance number from the Department of Health and Human Services may be substituted for this list.
3. A copy of the formal written notification approval from the IRB to the investigator regarding approval of the investigator and protocol. The written notification is to be signed by the chairman or authorized designee and must specify the specific protocol. An IRB member may not vote on any research in which he or she is involved.
4. An IRB approved specimen copy of the Informed Consent Form and other adjunctive materials used in this study to elicit and record subject consent in compliance with Food and Drug Administration regulations.
5. An updated Curriculum Vitae of the responsible Principal investigator, all sub-investigators or individuals listed on the FDA 1572 form.
6. Signed and dated Investigator Agreement or protocol signature page (Section 2.6).
7. Copy of laboratory license (eg. CLIA license) and laboratory normal values for any laboratory tests performed for the protocol
8. IRB Approved Advertising texts used for subject recruitment.

Protocol No. 99-001-P

August 20, 1999

1.8

ACCEPTABILITY OF CASE REPORT FORMS

Case report forms are provided for each subject. All forms must be filled out neatly in black ink or typed. The investigator will sign and date the appropriate signature pages upon completion.

Corrections of data on the case report forms may be made only by crossing out (using a single line) the incorrect data and writing the correct entry next to those crossed out. All corrections must have the initials and date of the person making the data change. No Advanced Care Products personnel or their representatives will be permitted to write on the original case report forms.

Completed case reports will be submitted to Advanced Care Products, Personal Products Corporation, pursuant to instructions. Case reports will be reviewed by the Advanced Care Products monitor, who will make a decision as to their acceptability.

1.9

MONITORING/ON-SITE AUDITS

The study will be initiated by the medical monitor (or designee) after all required documents have been processed. The investigator and the clinical site will be visited by an ACP monitor and/or an ACP auditor during the course of the study as frequently as it deems necessary. The first monitoring visit will usually be made as soon as possible after enrollment has been initiated. At this visit the monitor will compare the data entered in the case report forms with the hospital and clinic records (source documents). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow up of adverse events, administration of concomitant medication, drug receipt/dispensing/return records, and study drug administration information. Specific items required as source documents will be reviewed with the investigator prior to the study. Test articles and storage facilities will be inspected and inventoried for accuracy. As deemed appropriate, Advanced Care Products Research Quality Assurance personnel may conduct an audit of the clinical study site. The auditor may request access to all study records (including medical records) and any other source documents for reviewing purposes. The United States Food and Drug Administration (FDA), in the person of a trained and properly authorized employee of the Agency, may also request access to all study records, including source documents, for inspection and copying.

Protocol No. 99-001-P

August 20, 1999

2.0**SAMPLE SIZE**

There is no historical data available for this type of study. A pain study with a similar primary efficacy parameter, overall assessment, was used to estimate the sample size. A sample size of 35 subjects per treatment group will provide 80% power (at $\alpha=0.05$ level) to detect a 20% difference in the mean assessment score between phenazopyridine hydrochloride and placebo, assuming a standard deviation 1.3. Assuming 5 subjects per treatment group will drop out of the study, a sample size of 80 (40 per group) will be required.

2.1**STATISTICAL PROCEDURES****2.1.1 EFFICACY: Primary and Secondary Measures**

The objective of the efficacy analysis is to demonstrate the analgesic superiority of phenazopyridine hydrochloride to placebo. The primary analysis will be based on the intent-to-treat population. All subjects with dysuria, relief and overall assessments after dosing will be evaluable for efficacy.

The efficacy evaluations are as follows:

- Overall subject assessment of therapy, recorded as 1=poor, 2=fair, 3=good, 4=very good or 5=excellent
- Time to complete relief of general discomfort
- Dysuria relief as compared to baseline level and recorded as: 0=none, 1=little, 2=some, 3=a lot, or 4=complete
- Average volume per void
- Number of voids per subject
- Drug effect duration

The primary measure of overall analgesic efficacy will be the overall assessment of therapy. The overall assessment of therapy will be compared between phenazopyridine hydrochloride and placebo using the ANOVA procedure.

The time to relief of general discomfort will be analyzed using the Kaplan-Meier technique. The treatments will be compared using the Wilcoxon test available in the SAS LIFETEST procedure.

Protocol No. 99-001-P**August 20, 1999**

Dysuria relief will be compared between the two treatment groups.

The average volume per void, number of voids per subject and the duration of the drug's effect will be calculated for each treatment group and compared using two-sample t-tests.

Additional analyses may be conducted on the overall assessment by stratifying on baseline severity.

If normal assumptions are not met, then nonparametric methods will be performed. All tests will be two-sided at the 0.05 level of significance.

**2.1.2 SAFETY
 Adverse Experiences**

Safety evaluations will be based on the incidence and type of adverse experiences reported.

2.2 USE OF INFORMATION AND PUBLICATION

All information concerning the study and Advanced Care Products operations are considered confidential by Advanced Care Products and shall remain the sole property of Advanced Care Products. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without Advanced Care Products' written consent.

It is understood by the investigator that the information developed in the clinical study will be used by Advanced Care Products, and may be disclosed as required to other clinical investigators, to the U.S. Food and Drug Administration and to other government agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide Advanced Care Products complete test results and all data developed in this study.

2.3 DISPOSITION OF STUDY MATERIALS

All study materials received and dispensed by the investigator will be inventoried and accounted for throughout the study. The study materials will be stored in a secured area with restricted access.

Protocol No. 99-001-P**August 20, 1999**

The study monitor will arrange to return all used study medication boxes and unused study medication to:

Advanced Care Products
Clinical Packaging
691 US Highway 1 South
North Brunswick, NJ 08902

The investigator agrees not to supply the study material(s) to any person except those named as subinvestigator(s) on the FDA Form 1572 and subjects in this study. The investigator agrees not to use the study materials for non-study purposes, nor store it at any other site than those listed on the FDA Form 1572.

2.4**COMPLETION OF STUDY**

The investigator will complete and report (submission of CRFs) his/her study in satisfactory compliance with the protocol within the agreed upon time span. Continuation of this study beyond that time must be mutually agreed upon in writing by both the investigator and the sponsor, Advanced Care Products. It is agreed that, for reasonable cause, either the investigator or the sponsor, Advanced Care Products, may terminate this study before the agreed upon time span, provided a written notice is submitted at a reasonable time in advance of intended termination.

2.5**RECORDS RETENTION**

Federal law requires that all case report forms and a copy of all records (e.g., informed consent forms, laboratory reports, source documents, study drug dispensing record, etc.) which support case records of this study must be retained in the files of the responsible investigator for a minimum of two years after study is complete or discontinued. If the responsible investigator retires, relocates or withdraws from this responsibility, custody may be transferred to a person who will accept the responsibility. Advanced Care Products must be notified in writing of the name and address of the new custodian.

Protocol No. 99-001-P

August 20, 1999

2.6 INVESTIGATOR AGREEMENT

I have read the forgoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study medication and the conduct of the study.

I will use only the approved informed consent and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board responsible for the study.

I further agree that ACP shall have access to any source documents from which case report form information may have been generated.

Investigator's Signature

Date

Name of Investigator (Type or Print)

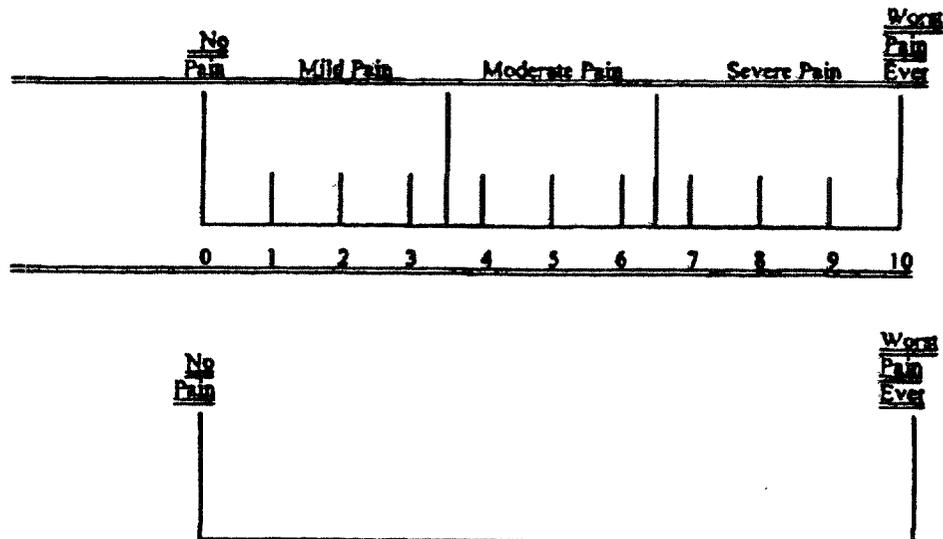
Protocol No. 99-001-P

August 20, 1999

2.7 ATTACHMENTS

- | | |
|-----------------|--------------------------------------|
| Attachment I: | Visual Analog Scale (VAS) |
| Attachment II: | Pain Severity and Relief Definitions |
| Attachment III: | Subject Instructions |
| Attachment IV: | Reference |
| Attachment V: | Package Insert Information |

**ATTACHMENT I
PROTOCOL 99-001-P
VISUAL ANALOG SCALE (VAS) AND PAIN SEVERITY DEFINITIONS**



Pain Severity Definitions:

Mild - a kind of pain you can't ignore, but not something you would normally take a medication for or treat unless it persisted.

Moderate - a pain level that would interfere with concentration; if you were trying to read or write, you might have to stop and take medication or treat the pain in some way.

Severe - a pain level that not only interferes with concentration but causes you to alter your behavior in some way. You might pace, fidget, go lie down, cry (whatever you do to cope with it). You would definitively feel that you need to treat the pain in some way.

**ATTACHMENT II
PROTOCOL 99-001-P**

RELIEF DEFINITIONS

Relief Definitions:

- | | |
|-------------------|---|
| No relief - | (0% gone) the same as your starting pain or worse |
| A little - | (25% reduction) less than half gone |
| Some relief - | (50% reduction) about half gone |
| Lot of relief - | (75% reduction) more than half gone |
| Complete relief - | (100% reduction) no pain |

**ATTACHMENT III
PROTOCOL 99-001-P**

SUBJECT INSTRUCTIONS

CONTENT OF STUDY MEDICATION BOX:

- 2 DARK BROWN TABLETS BLISTER-PACKED.

HOW TO TAKE THE STUDY MEDICATION

- REMOVE TABLETS FROM BLISTER PACK. SWALLOW THE 2 TABLETS WITH
8 OUNCES OF WATER

**ATTACHMENT IV
PROTOCOL 99-001-P**

REFERENCES

- Advanced Care Products, Research Report #TX-R-1720-1, Project #91-04, July 27, 1999
- Alano, F. A. and Webster, G. D. (1970). Acute renal Failure and Pigmentation due to Phenazopyridine (Pyridium). *Annals of Internal medicine* 72(1):89-91
- Cohen, B. L. and Bovasso, G. J. (1971) Acquired Methemoglobinemia and Hemolytic Anemia Following excessive Pyridium (Phenazopyridine Hydrochloride) Ingestion. *Clinical Pediatrics*. 10(9):537-540
- Gould, Stanley, MD. Clinical Comparison of Flavoxate and Phenazopyridine. *Urology* Vol. V, No. 5, May 1975
- IARC (1979). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
- Johnson, W. J. and Chartrand, A. (1976) The Metabolism and Excretion of Phenazopyridine Hydrochloride in Animals and Man. *Toxicology and Applied Pharmacology*. Vol. 37, 371-376
- Munday, R. and Fowke, E.A. (1994). Generation of Superoxide Radical and Hydrogen Peroxide by 2,3,6-Triaminopyridine, a Metabolite of the Urinary Tract Analgesic Phenazopyridine. *Free Radical Res.* 21(2):67-73.
- Slatter, D. H. and Davis, W. C. (1974). Toxicity of phenazopyridine. *Archives of Ophthalmology*. 91:484-486.
- Tiplady Brian., Jackson, Stephen H.D., Maskrey, Vivienne M. and Swift, Cameron G. Validity and sensitivity of visual analogue scales in young and older healthy subjects. *Age and Ageing*. 27:63-66, 1998.
- Trickett, Paul C, MD. Ancillary use of Phenazopyridine (Pyridium) in Urinary Tract Infections. *Current Therapeutic Research* Vol. 12, No. 7, July 1970
- Zelenitsky, S. A. and Zhanel, G. G. (1996). Phenazopyridine in Urinary Tract Infections. *The Annals of Pharmacotherapy* 30:866-868.

ATTACHMENT V
PROTOCOL 99-001-P

PACKAGE INSERT INFORMATION

ABOUT URINARY
DISCOMFORT AND:
URISTAT™

Phenazopyridine Hydrochloride 95 mg

THE #1 DOCTOR RECOMMENDED INGREDIENT
FOR URINARY PAIN RELIEF

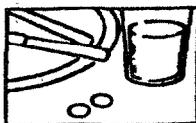
Nonprescription temporary pain relief – from the makers of MONISTAT®

URISTAT™ contains phenazopyridine HCl, the #1 doctor recommended medication used to treat pain or discomfort experienced while urinating.

Product Benefits

- Fast relief of pain, burning, urgency, and frequency of urination
- Easy-to-swallow tablet form
- Brought to you by the makers of MONISTAT® – the #1 recommendation of doctors and the #1 choice of women for vaginal yeast infections

NOTE: This product produces a harmless reddish-orange discoloration of the urine which may cause staining of clothing.

How To Use URISTAT™

For rapid relief of the symptoms of urinary discomfort:

- Take two tablets after meals, three times a day, as needed
- 2 days (up to 12 tablets) maximum

NOTE: Do not exceed 12 tablets per course of treatment.

Remember, URISTAT™ should only be used for temporary pain relief – it is not a cure. If symptoms are severe or persist, please call your doctor or clinician.

Treatment of a urinary tract infection with phenazopyridine HCl or a combination drug product containing phenazopyridine HCl should not exceed 2 days because there is a lack of evidence that the combined administration of phenazopyridine HCl and an anti-bacterial provides greater benefit than administration of the anti-bacterial alone after 2 days.

Warnings

- Do not take if you have previously exhibited hypersensitivity to phenazopyridine HCl or if you have kidney trouble. Remember that advanced age is associated with declining kidney function. Discontinue therapy if you experience a yellowish tinge of the skin or eyes. This may indicate accumulation due to impaired kidney or liver function.
- As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
- If your symptoms persist, are severe, or you experience fever, chills, back pain or bloody urine see your doctor promptly. You may have a serious condition that requires different treatment.
- Phenazopyridine HCl may cause gastrointestinal upset in some people. Take with or following meals to reduce gastric upset and discontinue use if symptoms occur.
- This product may stain soft contact lenses.
- Keep this and all drugs out of the reach of children and do not administer to children under the age of 12 unless directed by a physician.
- In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
- Carcinogenesis: Long-term administration of phenazopyridine HCl has induced neoplasia in rats (large intestine) and mice (liver). Although no association between phenazopyridine HCl and human neoplasia has been reported, adequate epidemiological studies along these lines have not been conducted.

**ATTACHMENT V
(CONTINUED)
PROTOCOL 99-001-P****PACKAGE INSERT INFORMATION****What is urinary discomfort?**

Simply put, urinary discomfort is pain during urination. Often described as a burning sensation, the pain can be severe and may affect the area under the stomach (the abdomen) or the lower back. Most people also feel a strong need to urinate more often or more urgently than usual, even though very little liquid is finally released.

UTIs: a common culprit

The most frequent cause of urinary discomfort is a urinary tract infection (sometimes called a bladder infection or cystitis). Urinary tract infections (UTIs) are not uncommon, especially in women. In fact, some women develop several UTIs within one year. It is important that you see your doctor or clinician whenever you have urinary discomfort. He or she will need to determine what is causing the pain before deciding how to treat it.

Attention to prevention: How to help avoid UTIs and urinary discomfort

While you'd probably prefer to avoid UTIs and urinary discomfort altogether, the good news is there are some steps you can take to help reduce your risks of infection and discomfort:

Dietary Factors

- Drinking six to eight glasses of water per day is a healthy practice for everyone, and it can help flush bacteria out of your bladder.
- Some foods may cause bladder irritation, and you may notice a connection. You may want to try reducing intake of some potentially irritating foods such as coffee, caffeinated/ carbonated beverages, alcohol and spicy or highly acidic foods such as tomatoes and citrus products.

Hygiene Factors

- Wiping from front to back after urinating can help prevent bacteria from entering the urethra. Also, urinating frequently may help. Don't resist the urge.
- During menstruation, change tampons or sanitary pads frequently to minimize bacterial growth.
- Taking showers instead of baths can wash bacteria away. Also, avoiding bubble bath products, douches, and scented soaps and toilet paper may reduce irritation.
- Wearing cotton underwear and avoiding tight clothing may help. Choosing unscented laundry detergents, bleaches, and fabric softeners can also reduce irritation.
- Urinating before and after sexual intercourse may also help in eliminating any bacteria. Washing the genital area before intercourse can also help.

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QUESTIONS?

URISTAT™ offers the only nurse-staffed answer line. CALL 1-800-582-6097

Appendix 2
Sample Case Report Form

ADVANCED CARE PRODUCTS:
Protocol No. 99-001-P

Phenazopyridine Hydrochloride

SUBJECT INITIALS:

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F M L

SUBJECT NUMBER:

| | | | | |
|--|--|--|--|--|
| | | | | |
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INVESTIGATOR NUMBER:

| | | | | | |
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Page 1

ADMISSION VISIT

Date of Visit (M/D/Y):

| | | |
|--|--|--|
| | | |
|--|--|--|

| DEMOGRAPHICS | | | | |
|---|--|--|--|--|
| Date of Birth (M/D/Y): <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> | | | | |
| | | | | |
| Race: <input type="checkbox"/> : Caucasian <input type="checkbox"/> : Black <input type="checkbox"/> : Asian <input type="checkbox"/> : Hispanic <input type="checkbox"/> : Other _____ | | | | |

| PHYSICAL EXAM | |
|--|-------|
| Significant Abnormality: <input type="checkbox"/> : No <input type="checkbox"/> : Yes, specify below | |
| 1. | _____ |
| 2. | _____ |
| 3. | _____ |

| PERTINENT MEDICAL HISTORY | | | | | | | |
|---|-------------|---------------|---|--|--|--|--|
| | Normal 1 | Abnormal 2 | Describe Abnormality (Diagnosis Where Possible) | | | | |
| 1. Recurring or Present Illness or Conditions at Baseline | | | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> </table> | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| 2. Genito-Urinary including G.U. Surgery | | | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> <tr><td style="height: 20px;"></td></tr> </table> | | | | |
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ADVANCED CARE PRODUCTS:
Protocol No. 99-001-P

Phenazopyridine Hydrochloride

SUBJECT INITIALS
F M L

SUBJECT NUMBER

Page 2

| SUBJECT SYMPTOMS AT BASELINE VISUAL ANALOG SCORE | |
|---|--|
| _____ | General Discomfort (if ≤ 3 do not enroll) |
| _____ | Urgency to Void (if ≤ 2 do not enroll) |
| _____ | Dysuria (if ≤ 2 do not enroll) |
| _____ | Total Score (if < 7 , DO NOT ENROLL) |

| LABORATORY RESULTS | |
|--------------------|--|
| Urine Dip Stick: | <input type="checkbox"/> : Positive <input type="checkbox"/> : Negative (if negative, do not enroll) |
| Pregnancy Test: | <input type="checkbox"/> : Negative <input type="checkbox"/> : Positive (if positive, do not enroll) |

| SUBJECT EVALUATION | |
|---------------------|---|
| Time of Void: | _____ am / pm (immediately prior to administration of study medication) |
| Time of Study Dose: | _____ am / pm |

| | |
|--|--|
| Complete general comfort relief | <input type="checkbox"/> : No, was not obtained |
| | <input type="checkbox"/> : Yes, specify time _____ Hrs. _____ Min. (Obtain time from stopwatch) |
| Did general discomfort return during 6 hour study? (If supplemental medication was required, please complete Supplemental Medication Section on page 3.) | |
| | <input type="checkbox"/> : No <input type="checkbox"/> : Yes, specify time _____ am / pm |

ADVANCED CARE PRODUCTS:
Protocol No. 99-001-P

Phenazopyridine Hydrochloride

SUBJECT INITIALS

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SUBJECT NUMBER

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Page 3

| SUPPLEMENTAL MEDICATION | | | |
|---|--------------|---|--|
| Did Subject use supplemental medication during the 0-6 hour study? <input type="checkbox"/> : No <input type="checkbox"/> : Yes, list below | | | |
| Medication Taken | Time (am/pm) | Pain Type | VAS SCORE |
| | | <input type="checkbox"/> General Discomfort | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |
| | | <input type="checkbox"/> Dysuria | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |
| | | <input type="checkbox"/> General Discomfort | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |
| | | <input type="checkbox"/> Dysuria | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |
| | | <input type="checkbox"/> General Discomfort | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |
| | | <input type="checkbox"/> Dysuria | <table border="1" style="display: inline-table; width: 40px; height: 20px;"></table> VAS Score |

| EFFECT OF DYSURIA | | | | | | |
|-------------------|------------------|---------------|--------------|------------------|------------|--------------------------------|
| Number of Voids | Complete Relief, | A Lot Relief, | Some Relief, | A Little Relief, | No Relief, | Volume of Urine Collected (ml) |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
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| 12 | | | | | | |

ADVANCED CARE PRODUCTS:
Protocol No. 99-001-P

Phenazopyridine Hydrochloride

SUBJECT INITIALS
F M L

SUBJECT NUMBER

| ADVERSE EXPERIENCE(S) | | | | | | | | | |
|---|--|--|--------------------------------------|-----------------------|-----------------------------------|---------------------------------|--------------------------------------|----------|-----------------|
| Did the subject have any adverse experiences during the study? <input type="checkbox"/> No <input type="checkbox"/> Yes, list below | | | | | | | | | |
| ADVERSE EXPERIENCE | START DATE | STOP DATE | S E V E R I T Y | C A U S E | A C T I O N (S) | O U T C O M E | Therapy Given for this Adverse Event | | |
| | | | | | | | NO 1 | YES 2 | If yes, specify |
| | M / D / Y | M / D / Y | SEE CODES | | | | | | |
| 1. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |
| 2. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |
| 3. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |
| 4. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |
| 5. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |
| 6. | M / D / Y <input type="checkbox"/> continuing | M / D / Y <input type="checkbox"/> continuing | | | | | | | |

Use the following codes for entry in the appropriate columns.

SEVERITY
1 - Mild
2 - Moderate
3 - Severe

CAUSE (Study Drug Relationship)
1 - Not Related
2 - Unlikely
3 - Possible
4 - Probable
5 - Highly Probable

ACTION(S) REQUIRED (Enter all applicable)
0 - None
2 - Study Drug Discontinued
3 - Study Drug Regimen Interrupted
4 - Hospitalized
5 - Counteractive Medication
6 - Other (Specify below)

OUTCOME
1 - Recovered from Adverse Experience
2 - Death
3 - Uncertain; Lost To Follow-Up
4 - Ongoing

Comments: _____

ADVANCED CARE PRODUCTS:
Protocol No. 99-001-P

Phenazopyridine Hydrochloride

SUBJECT INITIALS:

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F M L

SUBJECT NUMBER:

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Page 5

| |
|---|
| SUBJECT'S OVERALL ASSESSMENT OF STUDY MEDICATION |
| <input type="checkbox"/> 1 Excellent <input type="checkbox"/> 2 Very Good <input type="checkbox"/> 3 Good <input type="checkbox"/> 4 Fair <input type="checkbox"/> 5 Poor |

| |
|---|
| COMPLETION / DISCONTINUATION |
| <input type="checkbox"/> 1 Completed |
| <input type="checkbox"/> 2 Discontinuation |
| <input type="checkbox"/> 1 Subject Request |
| <input type="checkbox"/> 2 Adverse Experience(s): Specify: _____ |
| <input type="checkbox"/> 3 Supplemental Medication(s): Specify: _____ |

| |
|--|
| Was follow-up contact made? <input type="checkbox"/> 1 Yes <input type="checkbox"/> 2 No |
| If no, please explain: _____ |

Attach Label from Box Here

| | |
|--|------------|
| INVESTIGATOR'S STATEMENT | |
| I certify that I have carefully verified all entries on this case record form. | |
| Investigator's Signature _____ | Date _____ |

Appendix 3

Investigators' Curricula Vitae; List of Significant Study Personnel

List of Significant Study Personnel

| Investigator Number | Study Personnel | Site |
|------------------------|---|--|
| 1160-1 | Principal Investigator: Larry Gilderman, DO Coordinator: Brian Gilderman | University Clinical Research Associates, Inc. 1150 North University Drive Pembroke Pines, FL 33024 |
| 1090-1 | Principal Investigator: Dan Henry, MD Coordinators: Janet Lewis Michaela Himmelberger | Clinical Research Advantage, Inc. Foothill Family Clinic 2295 Foothill Drive Salt Lake City, UT 84109 |
| 1119-1 | Principal Investigator: Kevin Patrick, MD Coordinator: Cheryl Pickern | San Diego State University Student Health Services 5500 Campanile Drive San Diego, CA 92182-4701 |

Appendix 4
Statistical Analysis

Statistical Analysis

of

Protocol 99-001-P

**Evaluation of the Efficacy of Phenazopyridine Hydrochloride
(Formula PD-F-0016) as a Urinary Analgesic in Women
With Urinary Tract Infections**

By

J. Richard Trout, Ph.D.

For

**Advanced Care Products
Personal Products Corporation**

October 23, 2000

Table of Contents

| | <u>Page Number</u> |
|---|--------------------|
| Objective | 1 |
| Study Design | 1 |
| Statistical Methods | 1 |
| Results | 3 |
| Disposition of Subjects | 3 |
| Demographic and Medical History Summary | 3 |
| Baseline Symptoms | 4 |
| Efficacy Results | 5 |
| Safety Results | 9 |
| Conclusions | 10 |
| Appendix Tables | |
| Figures | |
| Data Listings | |

Intext Tables

Table Number/Page Number

| | |
|--|-----|
| Subject Disposition | 1/3 |
| Demographic Summary | 2/4 |
| Mean Baseline Symptom Scores | 3/5 |
| Mean Overall Assessment of Therapy | 4/6 |
| Summary of Complete General Comfort Relief And Recurrence of Symptoms | 5/6 |
| Time to Complete General Comfort Relief (hours) . | 6/7 |
| Mean Dysuria Scores | 7/8 |
| Voiding Summary | 8/9 |

Appendix Tables

| | <u>Table Number</u> |
|---|---------------------|
| Summary of Subject Disposition | 1 |
| Summary of Baseline Demographics | 2 |
| Summary of Baseline Symptoms | 3 |
| Summary of Subject Evaluation | 4 |
| Summary of Voiding Data and Effect of Dysuria | 5 |
| Listing of Adverse Events | 6 |
| Summary of Overall Assessment | 7 |

Appendix Figures

| | <u>Figure Number</u> |
|------------------------------------|----------------------|
| Time to Symptom Relief | 1 |
| Dysuria Score by Void Number | 2 |

Data Listings

| | <u>Listing Number</u> |
|--|-----------------------|
| Admission and Demographic Data | 1 |
| Physical Exam | 2 |
| Medical History | 3 |
| Subject Symptoms at Baseline Visual Analog Score | 4 |
| Laboratory Results | 5 |
| Subject Evaluation | 6 |
| Supplemental Medication | 7 |
| Effect of Dysuria | 8 |
| Adverse Experiences | 9A-D |
| Adverse Experiences – Comments | 9E |
| Subject's Overall Assessment of Study Medication | 10 |
| Completion/Discontinuation | 11 |

Objective

The objective of this study was to evaluate the efficacy and safety of Phenazopyridine hydrochloride (Formula PD-F-0016) as a short term treatment of urinary symptoms associated with urinary tract infections in women.

Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled, single dose analgesic study. The study was conducted at three study centers with a total of 76 subjects randomized, 35 to the Phenazopyridine Hcl treatment group and 41 to the placebo treatment group. All subjects were seen and evaluated by the investigator during the baseline admission visit. Subjects were to be entered into the study if they met a baseline pain level of the Visual Analog Scale of at least: 3 for general discomfort, 2 for urgency to void, and 2 for dysuria. Additionally, the combined sum of baseline pain level must reach at least seven of the VAS. Once the eligibility criteria were met, the investigator or authorized designee worked closely with the subject to collect all efficacy parameters, including the collection of urine samples during the first six hours post-dosing. The subject was asked to void her bladder before taking the study medication. Subsequent voids and volume collected were assessed during the entire first six-hour post-dosing observation period. Therefore, the subject was required to remain at the study facility during the first six hours post-dosing. There was a follow-up contact (1-3 days post-dosing) in which the investigator or authorized designee reviewed with the subject whether her UTI condition resolved.

Statistical Methods

Treatment groups were compared with respect to baseline demographic and medical history variables to examine the comparability of patients assigned to these two groups. The treatment groups were compared with respect to quantitative measures, such as age, using a t-test and with respect to qualitative variables, such as race, using Fisher's exact test. Baseline symptom scores were analyzed using the analysis of variance. The model used for this analysis included treatment group and study center. In addition the treatment by study center interaction was examined. As it was found to be not statistically significant, it was excluded from the model used in the final analysis.

The primary efficacy variable is the overall assessment of therapy. This outcome was analyzed in two ways. In one analysis the outcome was scored from 1 to 5 (1=poor to 5=excellent). This score was analyzed using an analysis of variance. The model used for this analysis included treatment group and study center. In addition the treatment by study center interaction was examined. As it was found to be not statistically significant, it was excluded from the model used in the final analysis. The second analysis summarized the five categorical outcomes and these data were analyzed using the Cochran-Mantel-Haenszel test. Secondary efficacy variables consisted of the following: occurrence of complete general relief, time to complete general relief, recurrence of symptoms during the 6 hour period, dysuria (mean relief score, first relief score, and last relief score), and voiding data (number of voids and average urine voiding volume). The treatment groups were compared with respect to the occurrence of complete general relief and the recurrence of symptoms during the 6 hour period using Fisher's exact test. The time to complete general relief was analyzed in two ways. First, for those subjects for whom complete general relief was achieved, the time to this event was analyzed using an analysis of variance. The model used for this analysis included treatment group and study center. In addition the treatment by study center interaction was examined. As it was found to be not statistically significant, it was excluded from the model used in the final analysis. The second method of analysis was based on survival methods. For those subjects for whom complete general relief was not achieved, the value of 6 hours was included and treated as a censored observation. That is, it was assumed that each subject was evaluated for 6 hours and that during this period complete general relief was not achieved. The treatment group comparison was based on both the Log-Rank test and the Wilcoxon test. Treatment group comparison for both dysuria and voiding data were based on the analysis of variance. The model used for this analysis included treatment group and study center. In addition the treatment by study center interaction was examined. As it was found to be not statistically significant, it was excluded from the model used in the final analysis.

Adverse events were summarized for each treatment group. However, since only twelve adverse events were noted, no statistical analysis was performed.

Statistical significance was declared if the two-sided p-value is ≤ 0.05 . All computations were performed using the Statistical Analysis System (SAS).

When the sample size was determined, there was no historical data available for this type of study. A pain study with a similar primary efficacy parameter, overall assessment, was used to estimate the sample size. A sample size of 35 subjects per treatment group provided 80% power (at the $\alpha=0.05$ level) to detect a 20% difference

in the mean assessment score between Phenazopyridine hydrochloride and placebo, assuming a standard deviation of 1.3. Assuming 5 subjects per treatment group drop out of the study, a sample size of 80 (40 per treatment group) was required.

Results

Disposition of Subjects

A total of 76 subjects were enrolled into the study. Thirty-five were randomized to Phenazopyridine Hcl and 41 were randomized to placebo. All subjects completed the study and are included in all analyses. The 76 subjects were recruited from three investigators. The number of subjects from each investigator for each treatment group is summarized in inext Table 1 and Appendix Table 1. Individual data are listed in Data Listings 1 and 11.

Table 1
Subject Disposition

| Investigator (Investigator Number) | Phenazopyridine Hcl | | Placebo | |
|--|------------------------|-----|---------|-----|
| | n | pct | n | pct |
| Henry (1090-1) | 11 | 31 | 16 | 39 |
| Patrick (1119-1) | 8 | 23 | 8 | 20 |
| Gilderman (1160-1) | 16 | 46 | 17 | 41 |
| Total | 35 | | 41 | |

Demographic and Medical History Summary

Subject demographic data are summarized in Appendix Table 2. No statistically significant differences between the treatment groups were found. Intext Table 2 summarizes subject's age and race. For those subjects randomized to Phenazopyridine Hcl the mean age was 31.8 years, with individual subjects ranging

in age from 15 to 67. The subjects in the placebo treatment group had a mean age of 32.6, with individual subjects ranging in age from 16 to 79.

Table 2
Demographic Summary

| Variable | | Phenazopyridine Hcl (n=35) | | Placebo (n=41) | |
|-------------|-----------|-------------------------------|------|-------------------|------|
| Age (years) | | 31.8 | | 32.6 | |
| Race | | n | pct | n | pct |
| | Caucasian | 24 | 68.6 | 30 | 73.2 |
| | Black | 3 | 8.6 | 8 | 19.5 |
| | Asian | 2 | 5.7 | 0 | 0.0 |
| | Hispanic | 6 | 17.1 | 3 | 7.3 |

Physical examination revealed that 5 (14.3%) subjects from the Phenazopyridine Hcl group a significant abnormality compared to 11 (26.8) subjects from the placebo group. Regarding medical history 18 (51.4%) of the subjects from the Phenazopyridine Hcl group had an abnormal illness or condition compared to 23 (56.1%) of the subjects in the placebo group. Abnormal genito-urinary medical history was found for 12 (34.3%) subjects in the Phenazopyridine Hcl group and 19 (46.3%) subjects in the placebo group. All subjects had a positive urine dip stick and had either a negative pregnancy test or did not require a pregnancy test.

The individual demographic, physical examination, and medical history data are listed in Data Listings 1 through 3 and Data Listing 5.

Baseline Symptoms

Subject baseline symptom data are summarized in Appendix Table 3. No statistically significant differences between the treatment groups were found. Intext Table 3 summarizes the mean score each symptom as well as the total score. For those subjects randomized to Phenazopyridine Hcl the mean general discomfort score was

6.3, the mean urgency to void was 7.2, the mean dysuria was 7.3, and the mean total score was 20.8. The subjects in the placebo treatment group had a mean general discomfort score of 6.4, a mean urgency to void of 6.9, a mean dysuria of 7.0, and a mean total score of 20.2. All subjects met the minimum scores required for inclusion in the study.

The individual data are listed in Data Listing 4.

Table 3
Mean Baseline Symptom Scores

| Variable | Phenazopyridine Hcl (n=35) | Placebo (n=41) |
|--------------------|----------------------------|----------------|
| General Discomfort | 6.3 | 6.4 |
| Urgency to Void | 7.2 | 6.9 |
| Dysuria | 7.3 | 7.0 |
| Total Score | 20.8 | 20.2 |

Efficacy Results

The primary efficacy variable was the overall assessment of therapy. Intext Table 4 and Appendix Table 7 summarize the results of these analyses. In this analysis the outcome was scored from 1 to 5 (1=poor to 5=excellent). The analysis shows that mean score for the Phenazopyridine Hcl treatment group was 3.6 and for the placebo group the mean was 2.6. The difference between the treatment groups was statistically significant ($p=0.0004$). When summarizing the individual outcomes, the analysis shows that 11 subjects (31.4%) rated the Phenazopyridine Hcl treatment as excellent compared to 2 (4.9%) subjects from the placebo group. At the other-end of the scale no subjects rated Phenazopyridine Hcl as poor compared to 9 (22.0%) subjects from the placebo group. Based on the individual ratings the treatment group difference was also statistically significant ($p=0.001$).

The individual data are listed in Data Listing 10.

Table 4
Mean Overall Assessment of Therapy

| Variable | Phenazopyridine Hcl (n=35) | Placebo (n=41) |
|-----------------------|----------------------------------|-------------------|
| Overall Assessment | 3.6 | 2.6 |

One group of secondary efficacy variables was the complete general comfort relief and the recurrence of symptoms. Intext Table 5 and Appendix Table 4 summarize the results of these analyses. The analysis shows that 14 (40.0%) of the subjects in the Phenazopyridine group experienced complete relief compared to 3 (7.3%) of the subjects in the placebo group. The difference between the treatment groups was statistically significant ($p=0.0008$). Among the subjects who experienced complete relief, 4 (28.6%) subjects in the Phenazopyridine group and 0 (0.0%) in the placebo group experienced a recurrence of symptoms. The treatment group difference was not statistically significant ($p=0.54$).

The individual data are listed in Data Listing 6.

Table 5
Summary of Complete General Comfort Relief and Recurrence of Symptoms

| Variable | Phenazopyridine Hcl | | Placebo | |
|---------------------------|------------------------|------|---------|-----|
| | n/N | pct | n/N | pct |
| Complete Relief | 14/35 | 40.0 | 3/41 | 7.3 |
| Recurrence of Symptoms | 4/14 | 28.6 | 0/3 | 0.0 |

Another secondary efficacy variable was the time to complete general comfort relief. Intext Table 6 and Appendix Table 4 summarize the results of the analysis of this variable. Using survival methods the analysis shows the mean time to complete relief was 4.9 hours compared to 5.8 hours for the placebo group. The difference between the treatment groups was statistically significant ($p < 0.0004$). These data are graphically summarized in Figure 1. Among the subjects who experienced complete relief the mean time to complete relief was 3.2 hours compared to 5.2 hours for the placebo group. The difference between the treatment groups approached statistically significant ($p = 0.0662$).

The individual data are listed in Data Listing 6.

Table 6
Time to Complete General Comfort Relief (hours)

| Variable | Phenazopyridine Hcl | Placebo |
|---|---------------------|---------------|
| Overall Assessment (Based on Survival Methods) | 4.9 (n=35) | 5.8 (n=41) |
| Overall Assessment (Based on Complete Relief Subjects Only) | 3.2 (n=14) | 5.2 (n=3) |

A secondary efficacy variable related to the effect of the treatment on dysuria. Intext Table 7 and Appendix Table 5 summarize the results of the analysis of dysuria. Three measures associated with the dysuria score (1=no relief to 5=complete relief) were analyzed. For each subject the mean score associated with all voids during the six hour period was determined. In addition, the score given at the first void and the score given at the last void was also determined. The analysis shows that the mean for the subjects treated with Phenazopyridine group was higher than that for subjects treated with placebo. For the mean relief score for all voids, the response for the

Phenazopyridine Hcl group was 3.0 compared to 2.4 for the placebo group. The difference between the treatment groups was statistically significant ($p=0.0011$). For the subjects in the Phenazopyridine group the mean dysuria score was 1.9 for the first void and 3.5 for the last void. In the placebo group these means were 1.6 and 2.9, respectively. The treatment group difference was not statistically significant ($p=0.18$) for the first void but was statistically significant for the last void ($p=0.02$). Figure 2 summarizes the dysuria (mean \pm standard error) for each void. When viewing this graph it should be remembered that the number of subjects becomes smaller as the void number increases.

The individual data are listed in Data Listing 8.

Table 7
Mean Dysuria Scores

| Variable | Phenazopyridine Hcl (n=35) | Placebo (n=41) |
|--------------------------|----------------------------------|-------------------|
| Mean Across All Voids | 3.0 | 2.4 |
| First Void | 1.9 | 1.6 |
| Last Void | 3.5 | 2.9 |

For each subject the number of voids and the average urine volume voided was determined. In-text Table 8 and Appendix Table 5 summarize the results of the analysis of dysuria. The analysis shows that the mean number of voids for the subjects treated with Phenazopyridine group was 5.7 compared to 5.1 for subjects in the placebo group. The difference between the treatment groups was not statistically significant ($p=0.33$). For the subjects in the Phenazopyridine group the mean urine volume per void was 108.3 ml while the subjects in the placebo group experienced a mean urine volume of 119.3 ml per void. The treatment group difference was not statistically significant ($p=0.74$). Appendix Table 5 also shows the frequency distribution for the number of voids per subject. The most frequently occurring number of voids was 4 and 5 for the Phenazopyridine group, both having a frequency

of 8 subjects, while 4 was the most frequently occurring number for the placebo group, with 12 subjects having this number of voids.

The individual data are listed in Data Listing 8.

Table 8
Voiding Summary

| Variable | Phenazopyridine Hcl (n=35) | Placebo (n=41) |
|-----------------------------------|----------------------------|----------------|
| Mean Number Of Voids In Six Hours | 5.7 | 5.1 |
| Mean Urine Volume Per Void | 108.3 | 119.3 |

As is shown in Data Listing 7, no subject used supplementation medication during the six hour study period.

Safety Results

A summary of the adverse events is given in Appendix Table 6. Individual data are shown in Data Listings 9A through 9E. Adverse events were recorded for four subjects in each treatment group. Only one of the adverse events, a kidney infection in a placebo treated subject, was considered severe. This event was considered to be not related to the treatment. The event that was reported most frequently was nausea. This event was reported in four subjects, three in the Phenazopyridine Hcl group and one in the placebo group. The only other event that occurred in more than one subject was a headache, which was reported in two placebo treated subjects.

Conclusions

The following conclusions can be reached with regard to this study to evaluate the efficacy and safety of Phenazopyridine hydrochloride (Formula PD-F-0016) as a short term treatment of urinary symptoms associated with urinary tract infections in women:

1. The treatment groups are well balanced with regard to demographic, medical history, and baseline variables.
2. The primary efficacy variable, the overall assessment of therapy, showed that Phenazopyridine Hcl was significantly better than placebo in relieving urinary symptoms associated with urinary tract infections.
3. Among the secondary efficacy variables, Phenazopyridine Hcl was found to be significantly better than placebo with respect to: occurrence of complete general comfort relief, time to complete general comfort relief, mean relief-dysuria score across all voids, and last void dysuria relief score.
4. Neither treatment group demonstrated any safety concerns. The event that was reported most frequently was nausea. This event was reported in four subjects, three in the Phenazopyridine Hcl group and one in the placebo group. The only other event that occurred in more than one subject was a headache, which was reported in two placebo treated subjects.

Appendix Tables

Advanced Care Products
Protocol No. 99-001-PTable 1
Summary of Subject Disposition

| Investigator (Number) | Treatment Groups | | Treatment Group Comparison P-Value |
|--------------------------|------------------------------------|------------------------|---|
| | Phenazopyridine Hcl n (percent) | Placebo n (percent) | |
| Henry (1090-1) | 11 (31.4) | 16 (39.0) | 0.83 ¹ |
| Patrick (1119-1) | 8 (22.9) | 8 (19.5) | |
| Gilderman (1160-1) | 16 (45.7) | 17 (41.4) | |
| Total | 35 | 41 | |

Note: All subjects completed the study.
One subject (604) in the Phenazopyridine Hcl group was not available for the follow-up contact.

¹ P-value based on Fisher's exact test.

Advanced Care Products
Protocol No. 99-001-PTable 2
Summary of Baseline Demographics

| Variable | Statistic | Treatment Groups | | Treatment Group Comparison P-Value |
|-------------|-----------|---------------------|---------|------------------------------------|
| | | Phenazopyridine Hcl | Placebo | |
| Age (years) | Mean | 31.8 | 32.6 | 0.81 ¹ |
| | Std | 12.8 | 14.9 | |
| | Min | 15 | 16 | |
| | Max | 67 | 79 | |
| | n | 35 | 41 | |

| Variable | Outcome | Treatment Groups | | Treatment Group Comparison P-Value |
|---|-----------|------------------------------------|------------------------|------------------------------------|
| | | Phenazopyridine Hcl n (percent) | Placebo n (percent) | |
| Race | Caucasian | 24 (68.6) | 30 (73.2) | 0.14 ² |
| | Black | 3 (8.6) | 8 (19.5) | |
| | Asian | 2 (5.7) | 0 (0.0) | |
| | Hispanic | 6 (17.1) | 3 (7.3) | |
| Physical Exam (Significant Abnormality) | No | 30 (85.7) | 30 (73.2) | 0.26 ² |
| | Yes | 5 (14.3) | 11 (26.8) | |
| Medical History (Illness or Condition) | Normal | 17 (48.6) | 18 (43.9) | 0.82 ² |
| | Abnormal | 18 (51.4) | 23 (56.1) | |
| Medical History (Genito-Urinary) | Normal | 23 (65.7) | 22 (53.7) | 0.35 ² |
| | Abnormal | 12 (34.3) | 19 (46.3) | |
| Urine Dip Stick | Positive | 35 (100) | 41 (100) | |
| | Negative | 0 (0.0) | 0 (0.0) | |
| Pregnancy Test | Negative | 32 (91.4) | 34 (82.9) | |
| | NA | 3 (8.6) | 7 (17.1) | |

¹ P-value based on t-test.² P-value based on Fisher's exact test.

Advanced Care Products
Protocol No. 99-001-PTable 3
Summary of Baseline Symptoms

| Variable | Statistic | Treatment Groups | | Treatment Group Comparison P-Value ¹ |
|--------------------|-----------|---------------------|---------|---|
| | | Phenazopyridine Hcl | Placebo | |
| General Discomfort | Mean | 6.3 | 6.4 | 0.79 |
| | Std | 1.6 | 1.8 | |
| | Min | 3.2 | 3.5 | |
| | Max | 10.0 | 9.9 | |
| | n | 35 | 41 | |
| Urgency to Void | Mean | 7.2 | 6.9 | 0.39 |
| | Std | 1.8 | 2.1 | |
| | Min | 2.5 | 2.0 | |
| | Max | 9.6 | 10.0 | |
| | n | 35 | 41 | |
| Dysuria | Mean | 7.3 | 7.0 | 0.48 |
| | Std | 2.0 | 1.9 | |
| | Min | 3.0 | 2.0 | |
| | Max | 9.8 | 9.9 | |
| | n | 35 | 41 | |
| Total Score | Mean | 20.8 | 20.2 | 0.57 |
| | Std | 4.2 | 4.7 | |
| | Min | 10.9 | 7.5 | |
| | Max | 28.9 | 28.0 | |
| | n | 35 | 41 | |

¹ P-value based on analysis of variance.

Advanced Care Products
Protocol No. 99-001-PTable 4
Summary of Subject Evaluation

| Variable | Outcome | Treatment Groups | | Treatment Group Comparison P-Value |
|---------------------------------|---------|------------------------------------|------------------------|------------------------------------|
| | | Phenazopyridine Hcl n (percent) | Placebo n (percent) | |
| Complete General Comfort Relief | Yes | 14 (40.0) | 3 (7.3) | 0.0008 ¹ |
| | No | 21 (60.0) | 38 (92.7) | |
| Recurrence of Symptoms | Yes | 4 (28.6) | 0 (0.0) | 0.54 ¹ |
| | No | 10 (71.4) | 3 (100) | |

| Variable | Statistic | Treatment Groups | | Treatment Group Comparison P-Value |
|--|-----------|---------------------|---------|------------------------------------|
| | | Phenazopyridine Hcl | Placebo | |
| Time to Complete General Comfort Relief (hours) | Mean | 3.2 | 5.2 | 0.0662 ² |
| | Std | 1.6 | 1.0 | |
| | Min | 1.0 | 4.0 | |
| | Max | 6.0 | 5.8 | |
| | n | 14 | 3 | |
| Time to Complete General Comfort Relief (hours) based on survival methods ⁵ | Mean | 4.9 | 5.8 | 0.0004 ³ |
| | n | 35 | 41 | |

¹ P-value based on Fisher's exact test.² P-value based on analysis of variance.³ P-value based on Log-Rank test.⁴ P-value based on Wilcoxon test.⁵ Censored observations set equal to 6 hours

Advanced Care Products
Protocol No. 99-001-PTable 5
Summary of Voiding Data and Effect of Dysuria

| Variable | Statistic | Treatment Groups | | Treatment Group Comparison P-Value ¹ |
|---|-----------|---------------------|---------|---|
| | | Phenazopyridine Hcl | Placebo | |
| Mean Relief Score Across All Voids ² | Mean | 3.0 | 2.4 | 0.0011 |
| | Std | 0.8 | 0.9 | |
| | Min | 1.7 | 1.0 | |
| | Max | 4.5 | 4.0 | |
| | n | 35 | 41 | |
| First Void Relief Score ² | Mean | 1.9 | 1.6 | 0.1773 |
| | Std | 1.0 | 0.9 | |
| | Min | 1.0 | 1.0 | |
| | Max | 4.0 | 4.0 | |
| | n | 35 | 41 | |
| Last Void Relief Score ² | Mean | 3.5 | 2.9 | 0.0218 |
| | Std | 1.1 | 1.2 | |
| | Min | 1.0 | 1.0 | |
| | Max | 5.0 | 5.0 | |
| | n | 35 | 41 | |
| Number of Voids in Six Hours | Mean | 5.7 | 5.1 | 0.3303 |
| | Std | 2.9 | 2.2 | |
| | Min | 2.0 | 2.0 | |
| | Max | 17.0 | 10.0 | |
| | n | 35 | 41 | |
| Urine Volume Per Void (ml) | Mean | 108.3 | 119.3 | 0.7386 |
| | Std | 63.0 | 88.2 | |
| | Min | 31.9 | 8.5 | |
| | Max | 355.0 | 367.5 | |
| | n | 35 | 41 | |

¹ P-value based on analysis of variance.² Scores are coded as follows: 1-no relief, 2-a little relief, 3-some relief, 4-a lot relief, 5-complete relief.

Advanced Care Products
Protocol No. 99-001-PTable 5
Summary of Voiding Data and Effect of Dysuria (cont.)

| <u>Variable</u> | <u>Outcome</u> | <u>Treatment Groups</u> | |
|-----------------|----------------|--|--------------------------------------|
| | | <u>Phenazopyridine Hcl</u> <u>n (percent)</u> | <u>Placebo</u> <u>n (percent)</u> |
| Number of Voids | 2 | 1 (2.9) | 3 (7.3) |
| | 3 | 5 (14.3) | 6 (14.6) |
| | 4 | 8 (22.9) | 12 (29.3) |
| | 5 | 8 (22.9) | 5 (12.2) |
| | 6 | 4 (11.4) | 5 (12.2) |
| | 7 | 2 (5.7) | 3 (7.3) |
| | 8 | 2 (5.7) | 3 (7.3) |
| | 9 | 3 (8.6) | 1 (2.4) |
| | 10 | 0 (0.0) | 3 (7.3) |
| | 12 | 1 (2.9) | 0 (0.0) |
| | 17 | 1 (2.9) | 0 (0.0) |

ADVANCED CARE PRODUCTS
 PROTOCOL NO. 99-001-P

TABLE 6
 LISTING OF ADVERSE EVENTS

| <u>TREATMENT GROUP</u> | <u>SUBJECT NUMBER</u> | <u>AE NUMBER</u> | <u>ADVERSE EXPERIENCE</u> | <u>SEVERITY</u> | <u>CAUSE</u> |
|------------------------|-----------------------|------------------|-----------------------------------|-----------------|--------------|
| PLACEBO | 101 | 1 | HEADACHE | MILD | POSSIBLE |
| PLACEBO | 202 | 1 | ITCHING-UPPER EXTREMITIES & CHEST | MODERATE | POSSIBLE |
| | | 2 | BUMPS-UPPER EXTREMITIES & CHEST | MODERATE | POSSIBLE |
| | | 3 | REDNESS-UPPER EXTREMITIES & CHEST | MODERATE | POSSIBLE |
| PLACEBO | 208 | 1 | KIDNEY INFLECTION | SEVERE | NOT RELATED |
| PLACEBO | 303 | 1 | HEADACHE | MILD | POSSIBLE |
| | | 2 | NAUSEA | MILD | POSSIBLE |
| PHENAZOPYRIDINE HCL | 201 | 1 | NAUSEA | MILD | PROBABLE |
| PHENAZOPYRIDINE HCL | 203 | 1 | HEARTBURN | MODERATE | POSSIBLE |
| PHENAZOPYRIDINE HCL | 204 | 1 | NAUSEA/VOMITING | MODERATE | UNLIKELY |
| | | 2 | LOW ABDOMEN PAIN | MODERATE | UNLIKELY |
| PHENAZOPYRIDINE HCL | 1002 | 1 | NAUSEA | MODERATE | PROBABLE |

Advanced Care Products
Protocol No. 99-001-PTable 7
Summary of Overall Assessment

| Variable | Outcome | Treatment Groups | | Treatment Group Comparison P-Value |
|--------------------|-----------|-----------------------------------|------------------------|------------------------------------|
| | | Penazopyridine Hcl n (percent) | Placebo n (percent) | |
| Overall Assessment | Poor | 0 (0.0) | 9 (22.0) | 0.001 ¹ |
| | Fair | 10 (28.6) | 12 (29.3) | |
| | Good | 6 (17.1) | 10 (24.4) | |
| | Very Good | 8 (22.9) | 8 (19.5) | |
| | Excellent | 11 (31.4) | 2 (4.9) | |

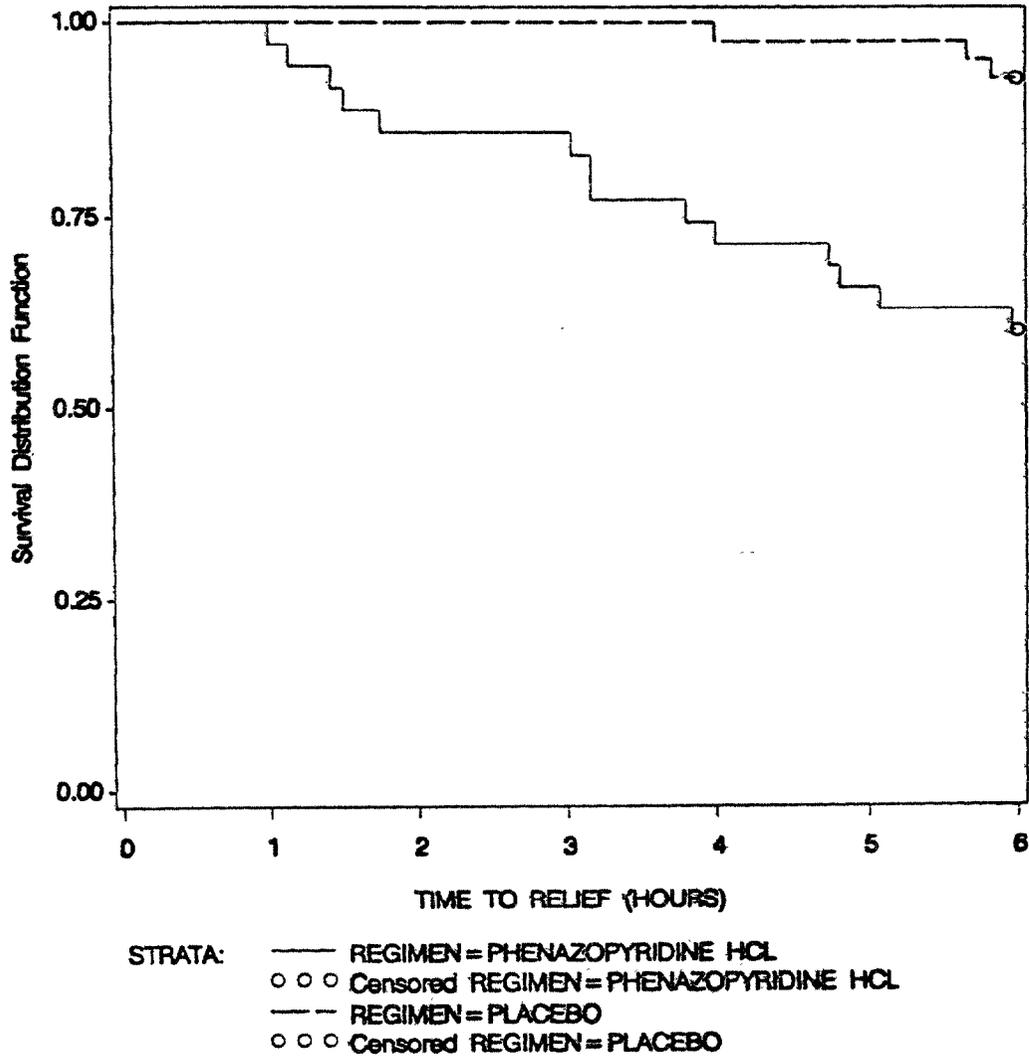
| Variable | Statistic | Treatment Groups | | Treatment Group Comparison P-Value |
|--------------------|-------------------|---------------------|---------|------------------------------------|
| | | Phenazopyridine Hcl | Placebo | |
| Overall Assessment | Mean ² | 3.6 | 2.6 | 0.0004 ³ |
| | Std | 1.2 | 1.2 | |
| | Min | 2.0 | 1.0 | |
| | Max | 5.0 | 5.0 | |
| | n | 35 | 41 | |

¹ P-value based on Cochran-Mantel-Haenszel.² Assessment scored as: 1=poor, 2=fair, 3=good, 4=very good, 5=excellent.³ P-value based on analysis of variance.

Figures

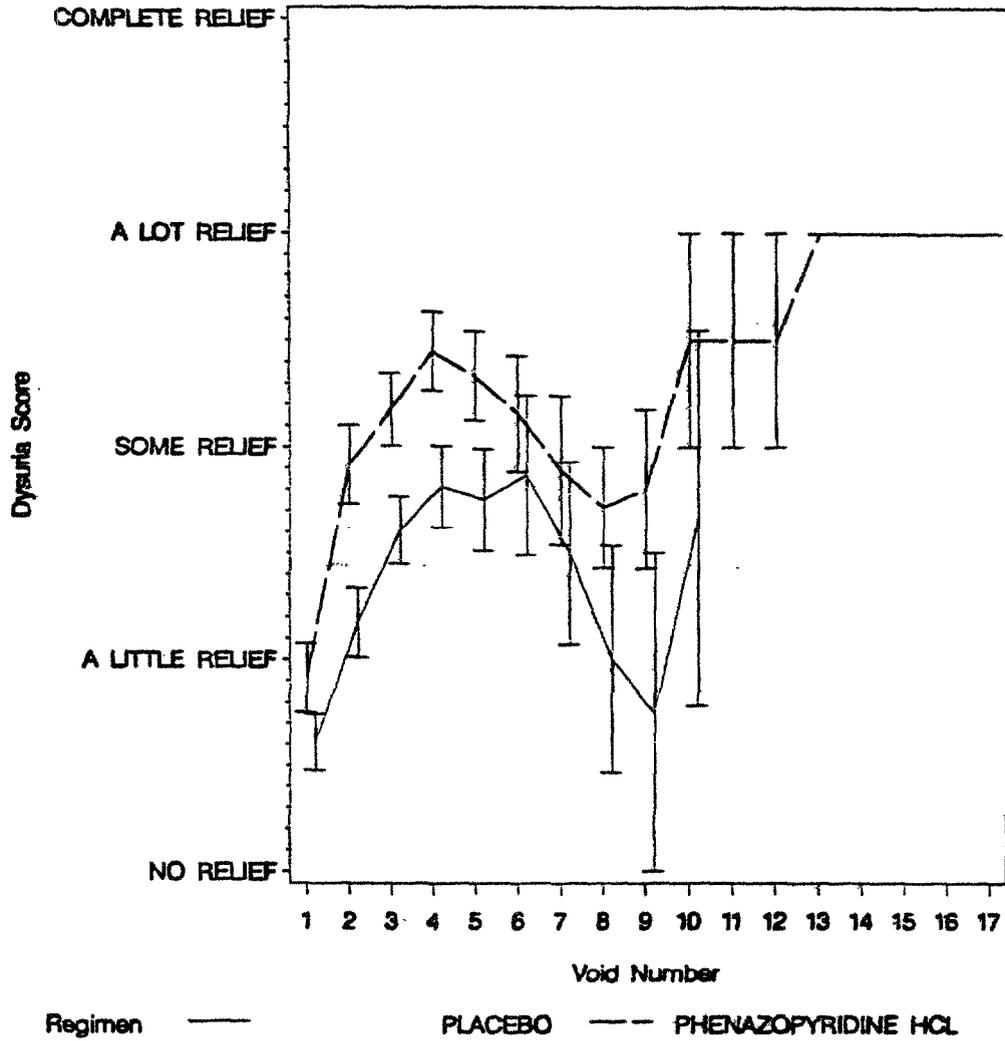
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FIGURE 1
TIME TO SYMPTOM RELIEF
SURVIVAL ANALYSIS USING 6 HOURS IF NO RELIEF IS FOUND



ADVANCED CARE PRODUCTS
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FIGURE 2
DYSURIA SCORE BY VOID NUMBER
MEAN \pm STANDARD ERROR FOR EACH TREATMENT REGIMEN



TABULATIONS