

Attachment 1

Department Number:  
Project Number:

## COMBINED CLINICAL/STATISTICAL SUMMARY

"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

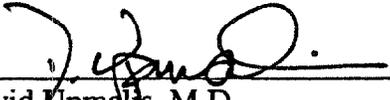
Report Number: 99-001-CR

Study Dates: October 21, 1999 to July 27, 2000

Sponsor Contact: David Upmalis, M.D.  
Executive Director, Clinical Affairs  
Personal Products Company

Date of Report: January 4, 2001

**Certification:** I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study, which was performed in compliance with good clinical practices and ethical principles consistent with the Declaration of Helsinki, as amended. Unless otherwise noted, informed consent was obtained in writing from all subjects at their first (screening) visit and prior to enrollment.

  
\_\_\_\_\_  
David Upmalis, M.D.  
Executive Director, Clinical Affairs

3/6/01  
\_\_\_\_\_  
Date

## SYNOPSIS

### Clinical Protocol Number: 99-001-P

**Date of Report:** January 4, 2001

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

**Sponsor:** Personal Products Company (formerly Advanced Care Products)

**Investigators and Centers:** Larry Gilderman, D.O.  
University Clinical Research Associates, Pembroke Pines, Florida

Dan Henry, M.D.  
Clinical Research Advantage, Inc., Salt Lake City, Utah

Kevin Patrick, M.D.  
San Diego State University Student Health Services, San Diego, California

**Study Period:** October 21, 1999 to July 27, 2000

**Objective:** To determine the efficacy of phenazopyridine hydrochloride 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, Phase IV single-dose outpatient study.

**Study Population:** Female subjects who were at least 12 years of age, in good health, and were not pregnant or nursing, were eligible to participate in this study. On the day of study dosing, all subjects were to have a confirmatory diagnosis of a symptomatic uncomplicated urinary tract infection (UTI) by urine dipstick and the presence of the qualifying type and severity of UTI symptoms using a Visual Analog Scale (VAS). Subjects were excluded from participation if they had prior use and knowledge of phenazopyridine hydrochloride (HCl) and its effect of urine discoloration, were sensitive to phenazopyridine HCl, used anti-infectives within seven days prior to, or over the counter (OTC) or prescription analgesics within twenty-four hours of, the day of study dosing, had a current history of renal or hepatic dysfunction, more than two documented UTIs that did not clear up with proper treatment, or a history of drug or alcohol abuse within six months prior to the study.

**Criteria for Evaluation of Drug Efficacy:** Baseline pain severity for UTI symptoms at admission was assessed by a VAS comprised of three pain definitions that corresponded to a zero to 10 number scale, with "mild" between 0 and 3.5, "moderate" between 3.5 and 6.5, and "severe" between 6.5 and 10. The extent of relief of the pain severity of dysuria at each void was assessed as complete, a lot, some, a little, or none compared to the subject's baseline pain on the VAS. The subject's overall assessment of therapy at six hours postdose was one of the following: excellent, very good, good, fair or poor.

**Criteria for Evaluation of Safety:** Safety was evaluated by the recording of all adverse events.

**Statistical Methods:** Treatment groups were compared with respect to baseline demographics and medical history variables using the t-test and Fisher's exact test. Comparison of baseline severity of symptoms between the two treatment groups were made using analysis of variance. The primary efficacy variable, the subject's overall assessment of therapy at six hours post dose, was analyzed using both analysis of variance and Cochran-Mantel-Haenszel tests.

**Results:** Seventy-six women were enrolled in the study; 35 received two tablets (95 mg each) of phenazopyridine HCl and 41 received two placebo tablets. Demographic and baseline characteristics were comparable in the two treatment groups. Statistical analysis of primary and secondary efficacy variables showed the phenazopyridine HCl was superior to placebo. Significantly more phenazopyridine HCl-treated subjects rated the overall assessment of therapy as excellent and experienced complete relief of general

discomfort during the six-hour postdose period. Relief of dysuria overall during this period was significantly greater for these subjects.

**Conclusions:**

Single-dose treatment with phenazopyridine HCl in women was safe and effective for relief of urinary symptoms associated with UTI, including general discomfort and dysuria.

**TABLE OF CONTENTS**

I.	<u>INTRODUCTION</u> .....	1
II.	<u>TEST MATERIALS</u> .....	1
III.	<u>STUDY OBJECTIVE</u> .....	2
IV.	<u>INVESTIGATIONAL PLAN</u> .....	2
	A. <u>Overall Design and Plan of Study</u> .....	2
	B. <u>Study Population</u> .....	3
	1. <u>Inclusion Criteria</u> .....	3
	2. <u>Exclusion Criteria</u> .....	3
	C. <u>Method of Assigning Subjects to Treatment Groups</u> .....	4
	D. <u>Effectiveness and Safety Variables Recorded and Data Quality Assurance</u> ...	5
	1. <u>Baseline Pain Severity of UTI Symptoms (VAS)</u> .....	6
	2. <u>Assessments During the Postdosing Period (0 to 6 hr)</u> .....	7
	3. <u>Mean Overall Assessment of Therapy</u> .....	7
	4. <u>Follow-Up Contact - Within 1 to 3 Days Postdosing</u> .....	8
	5. <u>Adverse Events</u> .....	8
	6. <u>Data Quality Assurance</u> .....	9
	E. <u>Concomitant Therapy</u> .....	10
	F. <u>Removal of Subjects From the Study or Analysis</u> .....	10
V.	<u>STATISTICAL METHODS</u> .....	10
VI.	<u>DISPOSITION OF SUBJECTS ENTERED</u> .....	12
	A. <u>Demographic and Baseline Characteristics of the Study Population</u> .....	12
	B. <u>Study Completion/Withdrawal Information</u> .....	14
	C. <u>Concomitant Therapy</u> .....	14
VII.	<u>RESULTS</u> .....	14
	A. <u>Efficacy Results</u> .....	14
	B. <u>Safety Results</u> .....	17
VIII.	<u>DISCUSSION</u> .....	19
IX.	<u>SUMMARY AND CONCLUSIONS</u> .....	20
X.	<u>REFERENCES</u> .....	21
XI.	<u>APPENDICES</u> .....	22

## TABLES IN TEXT

<b>TABLE</b>	<b>TITLE .....</b>	<b>PAGE</b>
Table I	Time and Events Schedule .....	6
Table II	Subject Disposition: All Subjects .....	12
Table III	Demographic and Baseline Characteristics: All Subjects .....	13
Table IV	Baseline Pain Severity of UTI Symptoms: All Subjects .....	14
Table V	Subject Assessment of Therapy: All Subjects .....	15
Table VI	Subject Evaluation of Relief of General Discomfort: All Subjects .....	16
Table VII	Voiding Data: All Subjects .....	17
Table VIII	Incidence of Adverse Events: All Subjects .....	18
Table IX	Subjects with Adverse Events .....	19

**LIST OF APPENDICES**

<b>APPENDIX</b>	<b>TITLE</b>	
Appendix 1	Study Protocol .....	23
Appendix 2	Sample Case Report Form.....	58
Appendix 3	Investigators' Curricula Vitae; List of Significant Study Personnel .....	64
Appendix 4	Statistical Analysis .....	69

**LIST OF TABULATIONS**

<b>TABLULATION</b>	<b>TITLE</b>	
Tabulation 1	Admission and Demographic Data.....	99
Tabulation 2	Physical Examination .....	102
Tabulation 3	Medical History .....	108
Tabulation 4	Symptoms at Baseline (Visual Analog Score) .....	120
Tabulation 5	Clinical Laboratory Results: Urine Dipstick and Pregnancy Test.....	123
Tabulation 6	Evaluation of Relief.....	126
Tabulation 7	Supplemental Medication .....	129
Tabulation 8	Effect on Dysuria by Subject.....	132
Tabulation 9A-9E	Treatment-Emergent Adverse Events.....	146
Tabulation 10	Overall Assessment of Study Medication by Subject.....	168
Tabulation 11	Completion/Discontinuation Information.....	171

## I. INTRODUCTION

Phenazopyridine hydrochloride (HCl), an azo dye, is the active ingredient in over-the-counter (OTC) medications for symptomatic relief of urinary tract infections (UTIs). It has been used in the United States as a urinary tract analgesic since 1914, and is still used widely for its local analgesic action on the urinary tract. Phenazopyridine HCl 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. Regardless of treatment with phenazopyridine HCl, however, the underlying cause of the urinary tract irritation must be determined and treated (e.g., antibacterial therapy for bacterial infection).

Phenazopyridine HCl tablets (doses less than 100 mg) have been available OTC since the 1960's. Currently phenazopyridine HCl products with doses of approximately 100 or 200 mg per tablet are available by prescription for use as a urinary tract analgesic.

Phenazopyridine HCl is a commercially available OTC urinary pain relief medication distributed by Personal Products Company (formerly Advanced Care Products) as URISTAT<sup>®</sup> (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, two tablets (95 mg per tablet), three times per day for a total of six tablets per day, not to exceed 12 tablets over a two-day period is safe and effective 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.

## II. TEST MATERIALS

The test product is phenazopyridine HCl (Formula No.: PD-F-0016), a 2,6-diamino-3-(phenylazo)pyridine monohydrochloride. The molecular weight is 249.70 and the empirical formula is C<sub>11</sub>H<sub>11</sub>N<sub>5</sub>.HCl. This azo dye is a light or dark red to dark violet, odorless, slightly bitter crystalline powder. The single dose consisting of two coated tablets of study medication contains approximately 53% w/w of phenazopyridine HCl, USP. Other ingredients present in the formulation are lactose hydrous, NF; sodium starch glycolate, NF; cornstarch, NF; hydrogenated vegetable oil (Sterotex K); colloidal silicon dioxide, NF and magnesium stearate, NF. The two study medication tablets are dark brown in color and blister-packed inside a white study medication box.

The placebo control in this clinical study is a single dose consisting of two coated tablets that contain no active ingredient (Formula No.: PD-F-1797) and that are identical in size and physical appearance to the active study medication.

All study medication was to be stored at room temperature.

### III. STUDY OBJECTIVE

The study objective was to determine the efficacy of phenazopyridine HCl as a short-term treatment of urinary symptoms associated with UTIs in women.

### IV. INVESTIGATIONAL PLAN

#### A. Overall Design and Plan of Study

This was a randomized, double-blind, parallel group, single dose, placebo-controlled study. Approximately 80 subjects with symptomatic uncomplicated UTI were to be enrolled, 40 subjects per treatment group. Subjects were to be randomly assigned to one of two orally administered, single-dose treatments:

- phenazopyridine HCl, consisting of two 95 mg tablets; or
- placebo, consisting of two tablets.

All subjects were to be seen and evaluated by the investigator during the baseline admission visit prior to study entry. If eligibility criteria were met, the subject (or the subject's guardian) was to sign an informed consent form, and was then to begin study participation. The subject's baseline symptoms (general discomfort, urgency to void, and dysuria) of the current episode of UTI were to be measured by means of a Visual Analog Scale (VAS) with 0 equal to no pain and 10 equal to the worst pain ever (see Attachment 1 of the protocol; Appendix 1 of this report). Before receiving study medication, the subject was to be asked to void her bladder. Immediately after voiding, the study medication, given with eight ounces of water, was to be administered by study site personnel. The subject was to remain at the study facility for the six-hour postdosing observation period. During this time, the subject was to report the number of subsequent voids, the volume per void and the extent of relief of dysuria (compared to baseline pain severity reported on the VAS) accompanying each void. Using a stopwatch or other similar device, the subject was also to measure the time to complete relief of the general discomfort recorded at baseline (no more general discomfort), and the time of subsequent recurrence of symptoms. Additional information including the subject's overall clinical progress and the occurrence of adverse events were also to be monitored during this time. At the end of the six-hour observation period, the subject was to make an overall assessment of therapy. Medical treatment for UTI was to begin after completion of the six-hour observation period.

In a follow-up contact (within three days postdosing) study site personnel were to ask each subject whether her UTI condition had resolved. Information on new adverse events and concomitant medication was to be

collected. The administration of the medication to treat the subject's UTI condition was also to be assessed and recorded.

## **B. Study Population**

### **1. Inclusion Criteria**

Female subjects who satisfied the following criteria were to be eligible for this study if they fulfilled all of the following criteria:

- 12 years of age or older (minors required parental or guardian consent);
- Not pregnant or nursing. A negative urine pregnancy test was to be obtained on the day of study medication dosing for all women of childbearing potential, including those who had had a tubal ligation;
- On the day of dosing, the subject reported or exhibited a baseline pain level as measured on the VAS of at least:
  - Three for general discomfort (overall assessment of the subject's symptomatology, which was to include pain in the lower abdominal section);
  - Two for urgency to void (urgent need to urinate, even when urine flow was minimal); and
  - Two for dysuria (pain at urination).

The sum of the three elements of baseline pain level listed above was to be at least seven;

- Confirmatory diagnosis of a symptomatic uncomplicated UTI by urine dipstick;
- 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; and
- Had signed (or guardian had signed) the informed consent form in which the subject agreed to participate after the study had been fully explained.

### **2. Exclusion Criteria**

Female subjects were not to be eligible for participation in the study if they fulfilled any of the following criteria:

- Prior use and knowledge of phenazopyridine HCl and its effect of urine discoloration;
- Use of any systemic anti-infective within seven days of admission;
- Use of any OTC or prescription analgesic within 24 hours of the day of study dosing;
- History of sensitivity to phenazopyridine HCl;
- Current history of renal dysfunction;
- Current history of hepatic dysfunction;
- Current history of diabetes;
- Had more than two documented UTIs within the past 12-month period or had a UTI that did not clear up with appropriate treatment;
- Was at risk in terms of the precautions, warnings, and contraindications in the package insert for phenazopyridine HCl;
- Was an employee of Johnson & Johnson, its affiliates, or employee of the clinical investigational site;
- Had a history of drug abuse or alcohol abuse within six months: or
- Was currently participating in a clinical trial or had received an experimental drug or used an experimental device in the last 30 days prior to admission into this study.

### **C. Method of Assigning Subjects to Treatment Groups**

A subject (parent or guardian, if the subject was a minor) who was interested in participating in the study was to be completely informed of the study requirements and procedures, including potential risks and benefits. Prior to entry into the study, potential subjects (or guardians) were to read and sign informed consent documents. Women of reproductive potential (including women with a tubal ligation) were to provide urine specimens to rule out pregnancy. The investigator was to perform a brief physical examination and, with the subject, was to assess the pain severity of the subject's symptoms to confirm the diagnosis of UTI. A urine dipstick test was also to be performed to confirm the diagnosis of UTI.

Only those subjects whose initial assessments did not have clinically significant results and who satisfied all of the study inclusion/exclusion criteria qualified for study participation. A sufficient number of women were to be enrolled to ensure that each of the two treatment groups included at least 35 subjects who completed the study.

Subjects were to be assigned drug according to a randomization schedule provided by Personal Products Company. Randomization was to be stratified to ensure an equal distribution of subjects to each arm of the study. Study medication was to be dispensed in sequential numerical order, starting with the lowest number.

**D. Effectiveness and Safety Variables Recorded and Data Quality Assurance**

Table I provides an overview of the study procedures. The text that follows the table provides more details about the procedures in the study and the variables that were recorded.

**Table 1**  
**Time and Events Schedule**  
**(Protocol 99-001-P)**

Procedure	Day 1		Days 2-4 <sup>e</sup>
	Pre-dose	0-6 Hrs Postdose	
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Review Concurrent Medications	X		
Obtain Pertinent Medical History <sup>b</sup>	X		
Assess/Record Baseline Symptoms (VAS) <sup>c</sup>	X		
Urine Dipstick Test <sup>d</sup>	X		
Urine Pregnancy Test <sup>e</sup>	X		
Brief Physical Exam	X		
Subject Voids Bladder <sup>f</sup>	X		
Remain Sequestered at Study Facility <sup>g</sup>		X	
Record Number and Volume of Voids		X	
Record Subject's Assessment of Dysuria for Each Void <sup>h</sup>		X	
Record Time to Complete Relief of General Discomfort <sup>i</sup>		X	
Record Subject's Overall Assessment of Therapy <sup>j</sup>		X	
Record Supplemental Medication <sup>k</sup>		X	
Record Concomitant Illnesses/ Adverse Events		X	X <sup>l</sup>
Begin Medical Treatment for UTI		X <sup>l</sup>	
Telephone Contact <sup>m,n</sup>			X

<sup>a</sup> Follow-up contact; telephone assessment made within three days after study drug administration.

<sup>b</sup> Recurring or present illnesses/conditions at baseline, and Genito-Urinary (G.U.) history including G.U. surgery.

<sup>c</sup> VAS to confirm diagnosis of symptomatic UTI.

<sup>d</sup> To confirm diagnosis of UTI.

<sup>e</sup> Including women with tubal ligation. FACT PLUS<sup>®</sup> was to be used to test for pregnancy or to be substituted by a test of equal or greater sensitivity.

<sup>f</sup> Immediately before study drug administration.

<sup>g</sup> Immediately after study drug administration. Subject was sequestered for six hours and was allowed to eat and drink "ad lib" during the six hours.

<sup>h</sup> Extent of relief of baseline pain severity for dysuria.

<sup>i</sup> Complete relief was defined as "no more" general discomfort. It was not required that a subject report complete relief during the six-hour postdosing period.

<sup>j</sup> To be selected from the following choices: excellent, very good, good, fair, or poor.

<sup>k</sup> Additional nonstudy analgesic, if required for relief of UTI symptoms.

<sup>l</sup> Treatment for UTI to begin after completion of the six-hour observation period.

<sup>m</sup> If a subject could not be reached for the follow-up contact, a registered letter with return receipt was to be sent requesting the follow-up information.

<sup>n</sup> To record medication taken to treat UTI and inquire about adverse events.

Cross-reference: Appendix 1

## 1. Baseline Pain Severity of UTI Symptoms (VAS)

Using a VAS numbered from 0 (no pain) to 10 (worst pain ever), the investigator was to assess, with the subject, the baseline pain severity of the UTI symptoms of general discomfort, urgency to void, and dysuria associated with the current episode of UTI. The VAS score was to be recorded in the source document at the study site and the numbers were to be transcribed onto the case report form (CRF). General discomfort was defined as an overall assessment of the subject's symptomatology, which may have included pain in the lower abdominal section. Dysuria was defined as pain during urination. Urgency to void was defined as an urgent need to urinate, even when urine flow was minimal. The VAS was comprised of three pain definitions that corresponded to a number scale of 0 to 10 (see Attachment 1 of the protocol, Appendix 1 of this report):

Score	Rating	Definition
0 to 3.5	Mild	A kind of pain you can't ignore, but not something you would normally take a medication for or treat unless it persisted.
3.5 to 6.5	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.
6.5 to 10	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 definitely feel you need to treat the pain in some way

## 2. Assessments During the Postdosing Period (0 to 6 hr)

The number and volumes of voids between 0 and 6 hours postdose were to be recorded on the subject's CRF. In addition, after each void, the subject was asked about the extent of relief of dysuria for that void, compared to the subject's baseline pain (mild, moderate or severe; 0 to 10 on the VAS). The subject was to evaluate the extent of relief experienced during each void based on the following five choices:

Relief Described as:	Reduction	Description
complete	100%	no pain
a lot	75%	more than half gone
some	50%	about half gone
little	25%	less than half gone
none	0%	same as or worse than starting pain

During the six-hour observation period, using a stopwatch or similar device, each subject was to specify the time when complete relief of general discomfort (compared to baseline VAS record) was obtained. If a subject reported complete relief of general discomfort during the six-hour period, and general discomfort subsequently returned during the six-hour period, the subject was to report the return of the symptom and the time of its return.

If supplemental analgesic was required by a subject during the six-hour observation period, the following data were to be recorded on the CRF: the time the analgesic was required; the pain type (general discomfort and/or dysuria); and pain severity as assessed by the VAS. If supplemental analgesic was required, the subject was to be withdrawn from the study.

## 3. Mean Overall Assessment of Therapy

At the end of the six-hour observation period, each subject was asked to make an overall assessment of therapy, choosing a response selected from the following choices: excellent, very good, good, fair, or poor.

Each subject was to be instructed to complete all information at the required times, as specified by the protocol, during the postdosing six-hour observation period. An authorized designee was to review and confirm the information with the subject and resolve any discrepancies before the subject left the study site. Measurements of general discomfort, urgency to void (number of voids and volume) and dysuria were to be recorded.

The investigator or authorized designee was to ask the subject for any complaints and adverse or unusual experiences; there were to be noted in the subject's chart. Adverse events were to be recorded in the CRF.

If supplemental analgesic medication was required at anytime during the first six-hour postdosing observation period, the reason it was required, the pain intensity (determined from the VAS) at the time it was required and the name of the medication were to be recorded in the source document, and the study subject was to discontinue participation in the study. The subject was to be encouraged (but not required) to wait at least four hours postdosing before taking supplemental pain medication, if there was no analgesic response to the study medication. The subject was to be encouraged (but not required) to wait until the pain level had returned to the baseline assessment before taking supplemental pain medication. A final assessment of current pain and relief from starting pain was to 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 occurred first, the subject was to make an overall assessment of the improvement (described as excellent, very good, good, fair, or poor) of her symptoms after taking the study medication.

#### **4. Follow-Up Contact - Within 1 to 3 Days Postdosing**

The subject was to be contacted within three days postdosing to determine resolution of the UTI. The incidence and severity of any adverse experience that may have occurred after the six-hour postdosing observation period and the administration of medication for the UTI were to be assessed.

If a subject could not be reached by telephone, a registered letter with return receipt was to be sent requesting the follow-up information.

#### **5. Adverse Events**

All new adverse experiences were to be recorded that were not present at baseline and that occurred during the six-hour

postdosing observation period or that were reported before the follow-up contact. An adverse event was any unwanted experience, including the deterioration of a medical condition that was present at baseline (prior to study dosing), whether or not the experience was related to study products or procedures. This included any side effect, toxicity, or sensitivity reaction to the products or procedures. This information was to be obtained by questioning and/or examining the subject during the six-hour postdosing observation period and at the follow-up contact.

Each adverse event was to be recorded on the CRF. The date of onset and resolution, the severity (mild, moderate, severe), the cause/study drug relationship (not related, unlikely, possible, probable, highly probable), the action(s) taken (none, study drug discontinued, study drug regimen interrupted, hospitalization, counteractive medication, other), the outcome (recovered, death, uncertain/lost to follow-up, ongoing), and therapy given for the adverse event were also to be recorded.

Any serious adverse event was to be reported to the sponsor immediately and subsequently in writing within five days of the occurrence. A serious adverse event was defined as any adverse event occurring that resulted in any of the following outcomes:

- Death;
- Life-threatening adverse drug experience;
- In-patient hospitalization or prolongation of existing hospitalization;
- Congenital anomaly/birth defect;
- Persistent or significant disability or incapacity;
- Important medical event: one that jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above.

## **6. Data Quality Assurance**

The investigator was to be visited by a monitor at study initiation and during the course of the study as deemed necessary. Monitoring visits were to include review of CRFs, source documents, and inspection of study drugs and storage facilities.

Data from each CRF were double-key entered into a database by the sponsor, and appropriate computer edit programs were run to

verify the accuracy of the database. Tabulations of the results were prepared by Personal Products Company, Skillman, NJ.

#### **E. Concomitant Therapy**

With the exception of analgesics or pain relievers, the use of concomitant medications was allowed during the study, and information concerning the concomitant medications was to be recorded on the source document. Use of any type of analgesic or pain reliever during the six-hour postdosing observation period was to result in the immediate discontinuation of the subject from the study. The reason an analgesic or pain reliever was required, the pain type (general discomfort and/or dysuria) and severity (determined using the VAS) at the time the analgesic or pain reliever was taken, and the name of the medication were to be recorded in the source document and on the CRF. The investigator was to notify the PPC monitor when this occurred.

#### **F. Removal of Subjects From the Study or Analysis**

Subjects were to be discontinued from the study for the following reasons:

- Subject request;
- Adverse experience(s); or
- Supplemental medication taken.

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

- Collection of all efficacy and safety information; and
- Completion of the discontinuation/completion form.

### **V. STATISTICAL METHODS**

All of the following analyses were performed by treatment group and study center. Since comparison of all variables by study center was not statistically significant, the final results for all analyses are presented by treatment group only (phenazopyridine HCl versus placebo).

Baseline demographic and medical history variables were used to assess the comparability of subjects assigned to the two treatment groups. Quantitated measurements, such as age, were analyzed using a t-test; qualitative variables, such as race, were analyzed using Fisher's Exact Test. Severity scores of baseline symptom pain were analyzed using the analysis of variance.

The primary efficacy variable was the subject's overall assessment of therapy. These data were analyzed in two ways. In one analysis, the assessment was scored on a numerical scale, from 1 to 5 (1 equal to poor and 5 equal to excellent), and

analyzed using an analysis of variance. For the second analysis, the five categorical outcomes were summarized by treatment group only; these data were analyzed using the Cochran-Mantel-Haenszel Test.

Secondary efficacy variables were the following:

- Occurrence of complete relief of general discomfort;
- Time to complete relief of general discomfort;
- Recurrence of symptoms during the six-hour period (for subjects who obtained complete relief);
- Extent of relief of dysuria (mean relief score for all voids, first void relief score, and last void relief score); and
- Voiding data (number of voids and average urine voiding volume).

The treatment groups were compared using Fisher's Exact Test with respect to the occurrence of complete relief of general discomfort and the subsequent recurrence of symptoms during the six-hour period. The time to complete relief of general discomfort was analyzed in two ways. First, for those subjects who obtained complete relief of general discomfort during the six-hour observation period, the time to this event was analyzed using an analysis of variance. The second method of analysis was based on survival methods. For each subject who did not obtain complete relief of general discomfort, the value of six hours was imputed and treated as a censored observation. That is, it was assumed that each of these subjects was evaluated for six 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 relief of dysuria and voiding data were based on the analysis of variance.

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 was  $\leq 0.05$ . All computations were performed using the Statistical Analysis System (SAS).

When the sample size was determined, there were no historical data available for this type of study. The sample size was estimated from the results of a pain study with a similar primary efficacy parameter, the subject's overall assessment. 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 HCl and placebo; a standard deviation of 1.3 was assumed. A sample size of 80 (40 per treatment group) was required, assuming that five subjects per treatment group would drop out of the study.

Safety evaluations were based on the incidence, type, and severity of adverse events. The proportions of subjects experiencing at least one adverse event and the proportion experiencing a given type of adverse event were calculated.

## VI. DISPOSITION OF SUBJECTS ENTERED

Seventy-six female subjects were enrolled in this study.

The disposition of subjects by investigator is shown in Table II. There were 35 subjects in the phenazopyridine HCl treatment group and 41 subjects in the placebo treatment group. Investigator Gilderman enrolled 33 subjects, investigator Henry enrolled 27 subjects, and investigator Patrick enrolled 16 subjects.

**Table II**  
**Subject Disposition: All Subjects**  
(Protocol 99-001-P – Phenazopyridine HCl Study)

Investigator (Number)	Treatment Group	
	Phenazopyridine HCl (N=35)	Placebo (N=41)
Henry (1090-1)	11 (31.0)	16 (39.0)
Patrick (1119-1)	8 (23.0)	8 (19.5)
Gilderman (1160-1)	16 (46.0)	17 (41.4)

Cross-reference: Appendix 4

### A. Demographic and Baseline Characteristics of the Study Population

Table III summarizes the demographic and baseline characteristics of the 76 subjects who participated in the study. No statistically significant differences between the treatment groups were found. Most (71.1%; 54/76) subjects were Caucasian; the remainder were Black (14.5%; 11/76), Hispanic (11.8%; 9/76), or Asian (2.6%; 2/76). There were more Hispanic subjects in the phenazopyridine HCl treatment group (17.1% versus 7.3%) and more Black subjects in the placebo treatment group (19.5% versus 7.3%). The mean age was 31.8 years in the phenazopyridine HCl treatment group (range, 15 to 67 years) and the mean age in the placebo treatment group was 32.6 years (range, 16 to 79 years). Five (14.3%) subjects in the phenazopyridine HCl treatment group and 11 (26.8%) subjects in the placebo treatment group had significant abnormalities reported during the physical examination. As seen in Tabulation 2, the significant medical abnormality of "suprapubic tenderness" was more prevalent in subjects in the placebo (19.5%; 8/41) treatment group compared to subjects (11.4%; 4/35) in the phenazopyridine HCl treatment group. All subjects had confirmation of UTI by a positive urine dipstick test and no subject was pregnant. The demographic characteristics of age and race by subject are provided in Tabulation 2. Physical examination and medical history abnormalities for all subjects are provided in Tabulations 2 and 3, respectively.

**Table III**  
**Demographic and Baseline Characteristics: All Subjects**  
**(Protocol 99-001-P – Phenazopyridine HCl Study)**

	Treatment Group					
	Phenazopyridine HCl (N=35)		Placebo (N=41)		Total (N=76)	
	n	(%)	n	(%)	n	(%)
<b>Race</b>						
Caucasian	24	(68.6)	30	(73.2)	54	(71.1)
Black	3	(8.6)	8	(19.5)	11	(14.5)
Asian	2	(5.7)	0	(0.0)	2	(2.6)
Hispanic	6	(17.1)	3	(7.3)	9	(11.8)
<b>Age (years)</b>						
Mean±SD	31.8±12.8		32.6±14.9			
Range	15-67		16-79			
<b>Physical Examination (Significant Abnormality)</b>						
No	30	(85.7)	30	(73.2)	60	(78.9)
Yes	5	(14.3)	11	(26.8)	16	(21.1)
<b>Medical History (Genito-Urinary)</b>						
Normal	23	(65.7)	22	(53.7)	45	(59.2)
Abnormal	12	(34.3)	19	(46.3)	31	(40.8)
<b>Urine Dipstick<sup>a</sup></b>						
Positive	35	(100.0)	41	(100.0)	76	(100.0)
Negative	0		0		0	
<b>Pregnancy Test<sup>b</sup></b>						
Negative	32	(91.4)	34	(82.9)	66	(86.8)
NA	3	(8.6)	7	(17.1)	10	(13.2)

<sup>a</sup> To confirm UTI diagnosis

<sup>b</sup> FACT PLUS<sup>®</sup> to be used as pregnancy test or a pregnancy test of equal or greater sensitivity

KEY: NA=not applicable

Cross-reference: Appendix 4; Tabulations 1 and 5

The baseline assessment of symptoms of UTI (as determined by VAS) for all subjects is summarized in Table IV. There were no statistical differences between treatment groups in baseline severity for the symptoms of general discomfort, urgency to void, or dysuria. All subjects met the inclusion requirement of a minimum sum of seven on the VAS of baseline symptom severity.

**Table IV**  
**Baseline Severity<sup>a</sup> of UTI Symptoms: All Subjects**  
**(Protocol 99-001-P – Phenazopyridine HCl Study)**

Symptom	Treatment Group		p-value <sup>b</sup>
	Phenazopyridine HCl (N=35)	Placebo (N=41)	
<b>General Discomfort<sup>c</sup></b>			
Mean±SD	6.3±1.6	6.4±1.8	0.79
Range	3.2-10.0	3.5-9.9	
<b>Urgency to Void<sup>d</sup></b>			
Mean±SD	7.2±1.8	6.9±2.1	0.39
Range	2.5-9.6	2.0-10.0	
<b>Dysuria<sup>e</sup></b>			
Mean±SD	7.3±2.0	7.0±1.9	0.48
Range	3.0-9.8	2.0-9.9	
<b>Total</b>			
Mean±SD	20.8±4.2	20.2±4.7	0.57
Range	10.9-28.9	7.5-28.0	

<sup>a</sup> As determined by VAS.

<sup>b</sup> Analysis of variance

<sup>c</sup> General discomfort was defined as an overall assessment of the subject's symptomatology, which may have included pain in the lower abdominal section.

<sup>d</sup> Urgency to void was defined as an urgent need to urinate, even when urine flow was minimal.

<sup>e</sup> Dysuria was defined as pain during urination.

Cross-reference: Appendix 4; Tabulation 4

## **B. Study Completion/Withdrawal Information**

All of the subjects completed the study (see Tabulation 11). One subject (604) completed the six-hour postdosing period, but follow-up contact with the subject within three days of postdosing was not made; a certified letter was sent, receipt was received, but the subject did not respond.

## **C. Concomitant Therapy**

None of the subjects took supplemental analgesics or any concomitant medication of clinical significance during the six-hour postdosing observation period

# **VII. RESULTS**

## **A. Efficacy Results**

The primary efficacy variable was the subject's overall assessment of therapy at six hours after study medication administration. Overall assessment was rated from 1 (poor) to 5 (excellent). As seen in Table V, the mean scores were 3.6 in the phenazopyridine HCl treatment group and 2.6 in the placebo treatment group. The difference in mean scores between treatment groups was statistically significant (p=0.0004). A placebo effect was observed; 73.2% (30/41) of subjects in the placebo group reported an

overall assessment of fair, good, or very good (versus 68.6% in the phenazopyridine HCl group); however eleven subjects (31.4%) in the phenazopyridine HCl treatment group rated the treatment as excellent, and only two subjects (4.9%) in the placebo treatment rated the treatment as excellent. No phenazopyridine HCl-treated subject rated the treatment as poor. In contrast, nine (22.0%) placebo-treated subjects rated the treatment as poor. To account for the discrete ordinal response (poor=1 to excellent=5) used in the analysis, the treatments were also compared using the Cochran-Mantel-Haenszel Test. The difference between treatment groups was statistically significant ( $p=0.001$ ).

**Table V**  
**Subject Assessment of Therapy: All Subjects**  
(Protocol 99-001-P – Phenazopyridine HCl Study)

	Treatment Group				p-value
	Phenazopyridine HCl (N=35)		Placebo (N=41)		
	n	(%)	n	(%)	
<b>Overall Assessment</b>					
Poor	0	(0.0)	9	(22.0)	0.001 <sup>e</sup>
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)	
<b>Score</b>					
Mean±SD <sup>b</sup>	3.6±1.2		2.6±1.2		0.0004 <sup>c</sup>
Range	2.0-5.0		1.0-5.0		

<sup>e</sup> Cochran-Mantel-Haenszel Test.

<sup>b</sup> Assessment coded as 1 (poor), 2 (fair), 3 (good), 4 (very good), or 5 (excellent).

<sup>c</sup> Analysis of variance.

Cross-reference: Appendix 4; Tabulation 10

Subject evaluation of complete relief of general discomfort is presented for all subjects in Table VI. Complete relief was experienced by 40.0% (14/35) phenazopyridine HCl-treated subjects with 71.4% (10/14) of these subjects reporting no recurrence of symptoms. By contrast, 7.3% (3/41) of placebo-treated subjects experienced complete relief; none of these three subjects reported recurrence of symptoms. The difference between treatment groups in the number of patients with complete relief was statistically significant ( $p=0.0008$ ).

The mean time to complete relief for phenazopyridine HCl-treated subjects was two hours less than for placebo-treated subjects ( $3.2\pm 1.6$  hours versus  $5.2\pm 1.0$  hours, respectively); however, this was not statistically significant ( $p=0.07$ ). When analysis of complete relief of general discomfort was analyzed using survival methods, the mean time to complete relief was 4.9 hours for phenazopyridine HCl-treated subjects and was 5.8 hours for placebo-treated subjects; this treatment difference was statistically significant ( $p=0.0004$  by the Log-Rank Test and  $p=0.0003$  by the Wilcoxon Test).

**Table VI**  
**Subject Evaluation of Relief of General Discomfort: All Subjects**  
**(Protocol 99-001-P – Phenazopyridine HCl Study)**

	Treatment Group				p-value
	Phenazopyridine HCl		Placebo		
	n	(%)	n	(%)	
<b>Complete Relief</b>					
N	35		41		
Yes	14	(40.0)	3	(7.3)	0.0008 <sup>a</sup>
No	21	(60.0)	38	(92.7)	
<b>Recurrence</b>					
N	14		3		
Yes	4	(28.6)	0	(0.0)	0.54 <sup>a</sup>
No	10	(71.4)	3	(100.0)	
<b>Time to Complete Relief (Hours)</b>					
N	14		3		
Mean±SD	3.2±1.6		5.2±1.0		0.0662 <sup>b</sup>
Range	1.0-6.0		4.0-5.8		
<b>Time to Complete Relief (Hours): Survival Method<sup>c</sup></b>					
N	35		41		
Mean	4.9		5.8		0.0004 <sup>d</sup> 0.0003 <sup>e</sup>

<sup>a</sup> Fisher's Exact Test

<sup>b</sup> Analysis of variance

<sup>c</sup> Censored observations assigned as equal to 6 hours

<sup>d</sup> Log-Rank Test

<sup>e</sup> Wilcoxon Test

Cross-reference: Appendix 4; Tabulation 6

Voiding data for all subjects are presented in Table VII. Relief from dysuria during each void was measured by scores assigned by the subject. As seen in the table, the mean scores for dysuria relief at the first void was comparable for both treatment groups. There was more relief at the last void (3.5±1.1) in the phenazopyridine HCl treatment group than in the placebo treatment group (2.9±1.2), and this difference was statistically significant (p=0.0218). The mean dysuria relief score for all voids during the six-hour observation period was 3.0±0.8 in the phenazopyridine HCl treatment group compared to 2.4±0.9 in the placebo treatment group; this difference was statistically significant (p=0.0011).

The mean number of voids and the mean volume of urine per void were comparable in the two treatment groups. Most subjects voided three to five times, with a range of 2 to 17 voids in the phenazopyridine HCl treatment group and 2 to 10 voids in the placebo treatment group.

**Table VII**  
**Voiding Data: All Subjects**  
**(Protocol 99-001-P – Phenazopyridine HCl Study)**

Variable	Treatment Group		p-value <sup>a</sup>
	Phenazopyridine HCl (N=35)	Placebo (N=41)	
<b>Relief Score<sup>b</sup></b>			
All voids in 6 hours totaled			
Mean	3.0±0.8	2.4±0.9	0.0011
Range	1.7-4.5	1.0-4.0	
First Void			
Mean	1.9±1.0	1.6±0.9	0.1773
Range	1.0-4.0	1.0-4.0	
Last Void			
Mean	3.5±1.1	2.9±1.2	0.0218
Range	1.0-5.0	1.0-5.0	
Number of Voids in 6 Hours			
Mean	5.7±2.9	5.1±2.2	0.3303
Range	2.0-17.0	2.0-10.0	
Urine Volume per Void (mLs)			
Mean	108.3±63.0	119.3±88.2	0.7386
Range	31.9-355.0	8.5-367.5	
Number of Voids (n[%])			
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)	

<sup>a</sup> Analysis of variance

<sup>b</sup> Scores coded as 1 (no relief), 2 (a little relief), 3 (some relief), 4 (a little relief), or 5 (complete relief).

Cross-reference: Appendix 4; Tabulation 8

## B. Safety Results

The incidence of all treatment-emergent adverse events is presented in Table VIII. These adverse events are presented by subject in Table IX. Four subjects in each treatment group experienced one or more adverse events. In the phenazopyridine HCl treatment group, 11.4% (4/35) experienced a total of five adverse events; Subject 204 experienced two events (nausea/vomiting and low abdomen pain) and Subjects 201, 203, and 1002 each experienced one adverse event (nausea, heartburn, and nausea, respectively). In the placebo treatment group, 9.8% (4/41) experienced seven adverse events, Subject 202 experienced three events (itching, bumps, and redness of the upper extremities and chest), Subject 303 experienced two events (headache and nausea), and Subjects 101 and 208 each experienced one event (headache and kidney infection, respectively). Seven adverse events were considered to be

possibly related to study medication. Nausea in two subjects (201 and 1002) in the phenazopyridine HCl treatment group were considered to be probably related to study medication; nausea/vomiting and low abdomen pain reported by Subject 204 in the phenazopyridine HCl treatment group were considered to be unlikely related to study medication. Kidney infection reported by Subject 208 in the placebo treatment group was considered to be not related to study medication. This subject did not take the antibiotic medication prescribed for UTI after the six hour observation period and was treated with intravenous Rocephin® in the emergency room the next day. The kidney infection was considered to be severe and lasted for four days. All other adverse events were either mild or moderate in severity. All subjects recovered without sequelae. No concomitant medication or supplemental medication (see Tabulation 7) was administered for any adverse event.

**Table VIII**  
**Incidence of Adverse Events: All Subjects**  
(Protocol 99-001-P – Phenazopyridine HCl Study)

	Treatment Group	
	Phenazopyridine HCl (N=35)	Placebo (N=41)
<b>Total With Adverse Events (%)</b>	4 (11.4)	4 (9.8)
<b>Total No. of Adverse Events</b>	5 (14.3)	7 (17.1)
<b>Adverse Event</b>		
Nausea or Nausea/Vomiting	3 (8.6)	1 (2.4)
Headache	0 (0.0)	2 (4.9)
Heartburn	1 (2.9)	0 (0.0)
Low Abdomen Pain	1 (2.9)	0 (0.0)
Kidney Infection <sup>a</sup>	0 (0.0)	1 (2.4)
Itching-Upper Extremities and Chest	0 (0.0)	1 (2.4)
Bumps-Upper Extremities and Chest	0 (0.0)	1 (2.4)
Redness-Upper Extremities and Chest	0 (0.0)	1 (2.4)

<sup>a</sup> Considered to be severe.

Cross-reference: Tabulation 9A-9E

**Table IX**  
**Subjects with Adverse Events**  
(Protocol 99-001-P – Phenazopyridine HCl Study)

Treatment Group Subject No.	Age (yrs)	Adverse Event	Duration (Days)	Severity	Relationship to Study Drug	Outcome
Phenazopyridine HCl						
201	24	Nausea	1	Mild	Probable	Recovered
203	36	Heartburn	1	Moderate	Possible	Recovered
204	17	Nausea/Vomiting Low Abdomen Pain	2	Moderate Moderate	Unlikely Unlikely	Recovered
1002	23	Nausea	1	Moderate	Probable	Recovered
Placebo						
101	35	Headache	1	Mild	Possible	Recovered
202	17	Itching - Upper Extremities and Chest Bumps - Upper Extremities and Chest Redness - Upper Extremities and Chest	1	Moderate Moderate Moderate	Possible Possible Possible	Recovered
208	32	Kidney Infection	4	Severe	Not Related	Recovered
303	20	Headache Nausea	1	Mild Mild	Possible Possible	Recovered

Cross-reference: Tabulation 9A-9E

## VIII. DISCUSSION

In this placebo-controlled study, phenazopyridine HCl or placebo was administered to 76 female subjects to determine efficacy of phenazopyridine HCl in the short-term treatment of urinary symptoms associated with UTIs in women. Subjects assessed the severity of their baseline UTI symptoms, consisting of general discomfort, urgency to void, and dysuria, by means of a VAS. During and after a six-hour observation period, subjects measured the number and volume of all voids, and assessed relief of dysuria. At the end of the six-hour observation period, each subject determined an overall assessment of therapy (the primary efficacy assessment).

Demographic and baseline characteristics of race and age were generally comparable between the treatment groups. Subjects in the placebo treatment group reported more suprapubic tenderness at the admission physical examination than did subjects in the phenazopyridine HCl treatment group. Although suprapubic tenderness is a symptom associated with UTIs, inspection of the efficacy data for these subjects revealed that this difference introduced no bias in the study results.

Statistical analyses of primary and secondary efficacy variables, including relief of general discomfort of UTIs, showed that treatment with phenazopyridine HCl was statistically better than treatment with placebo. Although a placebo effect was observed, mean scores of the subjects' overall assessments of therapy were statistically higher for the phenazopyridine HCl treatment group. More subjects (11/35; 31.4%) rated the treatment as excellent in the phenazopyridine HCl

treatment group than those in the placebo treatment group (2/41;4.9%). Complete relief of general discomfort was experienced by 14/35 (40.0%) phenazopyridine HCl-treated subjects, in contrast to 7.3% (3/41) of placebo-treated subjects; this difference between treatment groups was also statistically significant. When analyzed by survival methods, allowing inclusion of all subjects' responses (censored), the mean time to complete relief (4.9 hours, phenazopyridine HCl; 5.8 hours, placebo) was also statistically significant. In addition, the differences between treatment groups in the extent of relief of dysuria during the last void and for all voids overall during the six hours postdose period were statistically significant.

Safety results were unremarkable. Four subjects in each treatment group experienced one or more adverse events. Nausea was experienced by four subjects (three treated with phenazopyridine HCl and one treated with placebo), and was considered to be possibly or probably related to study medication in three subjects. Headache was experienced by two subjects in the placebo treatment group. One placebo-treated subject experienced a severe kidney infection, not considered to be related to study medication, and she recovered in four days. Other adverse events were experienced by only one subject.

## IX. SUMMARY AND CONCLUSIONS

Short-term treatment with phenazopyridine HCl in women was safe and effective for relief of urinary symptoms associated with UTI, including general discomfort and dysuria.

**X. 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.