# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-105**

# MEDICAL REVIEW

DEC 21 2000

**Medical Officer's Review of NDA 21-105: Zotrim™ UTI Therapy**
**(Combination blister pack of phenazopyridine hydrochloride & trimethoprim/sulfamethoxazole)**

**Sponsor:** Able Laboratories, Inc./DynaGen, Inc.
840 Memorial Drive
Cambridge, MA 02139

**Contact:** Peter J. Mione, MS, Vice-President, Clinical & Regulatory Affairs
Tel. 617-491-2527

**Date of Submission:** February 18, 1999
**Date of Amendment:** May 25, 2000
**Date Review Completed:** November 15, 2000

**Drug to be Combined In Blister Pack:** Zotrim™ UTI Therapy:
Trimethoprim-sulfamethoxazole, 160 mg/800 mg (1 po 2x day for 10 days)
Phenazopyridine hydrochloride, 200 mg (1 po 3x day for 2 days)

**Introduction:**

The Sponsor seeks approval for a blister pack containing the following three drugs: six tablets of phenazopyridine hydrochloride ("pyridium") 200 mg and 20 tablets of trimethoprim/sulfamethoxazole (TMP/SMX) DS 160 mg/800 mg in a fixed combination ("TMP-SMX").

The pack would be used to treat uncomplicated urinary tract infections in the following manner:
Pyridium, 1 tablet three times a day for two days
TMP/SMX, 1 tablet twice a day for ten days.

**Status of Component Drugs in the United States:**
All the components are currently marketed in this country. Pyridium is marketed as analgesia for pain of the urinary tract, and TMP/SMX is approved for the treatment of urinary tract infection. The Sponsor believes that the convenience of such a blister pack would increase compliance.

Pyridium is a pre-1938 drug with no existing FDA approval based upon a new drug application (NDA). This drug has been used as a urinary tract analgesic for over 40 years, and no recent adequate and well-controlled clinical trials exist that support its safety and efficacy. The Sponsor has submitted, as is required, literature supporting the safety and efficacy of pyridium. The literature is old and would not meet current FDA requirements for approval. However, as with products that have been introduced by monograph, we assume the product to be safe and effective unless there is evidence to the contrary.

FDA has approved TMP/SMX for the treatment of UTI in 10- and 14- day regimens. Although there are many reports in the literature to support shorter treatment for uncomplicated UTI, data has never been submitted to the FDA for review. Thus, the Sponsor was informed during a face-to-face meeting on March 10, 1997, that if a shorter treatment course of TMP/SMX would be sought, this would require that the application contain information demonstrating the safety and efficacy of a shorter course of TMP/SMX. This could take the form of a "paper" NDA. The Sponsor has not elected to seek a shorter course in this application.

TMP/SMX is also widely used to treat acute otitis media, acute exacerbations of chronic bronchitis, traveler's diarrhea in adults, shigellosis, and pneumonia caused by *Pneumocystis carinii*.

The Sponsor submitted this application as a nineteen-volume NDA based on review of safety and experimental publications. Four volumes constitute the clinical application. No clinical efficacy studies were undertaken for this application. A pharmacokinetic study, "A Randomized, Multiple-Dose, Two Way Crossover Drug Interaction Study in Healthy Female Subjects", was undertaken at the request of the

Division of Anti-Infective Drug Products' (DAIDP's) Biopharmaceutical Reviewer in an effort to detect whether there was any interaction when pyridium and TMP/SMX are taken together. See section headed "Pharmacokinetic Study", on page 3 of this review.

The combination of pyridium (400 mg) and sulfamethoxazole (2 gms) [redacted] is currently approved and marketed.

**Proposed labeling submitted by Sponsor:**
The Sponsor submitted labeling attached to this review as Appendix 1. Only those sections of the label relevant to the indication of uncomplicated UTI are submitted from the TMP/SMX label. The labels were excerpted from the 1997 and 1998 PDR. Thus, the most recent labels are not submitted in this application, and the Sponsor will be required to correct any changes that have occurred since 1998.

The Pharmacotoxicology Reviewer had the following comments: "...doses are expressed as mg/kg, different pregnancy categories (B and C) are used in different places, and the effects on nursing mothers are given only for one drug (pyridium) and not the others." Thus, the Precautions section of the label must be revised to correct these shortcomings, as recommended by the Pharmacotoxicology Reviewer.

Sections of the label derived from the pharmacokinetic study undertaken by the sponsor are discussed later in this review.

**Pharmacokinetic publications submitted for clinical review:**
Sponsor's Bibliography is attached as Appendix 2. The following studies are described in detail.

Kremers P, Duvivier J, Heusghem C. Pharmacokinetic Studies of CoTrimoxazole in Man After Single and Repeated Doses. J Clin Pharmacol 1974;14:112-117.

Schwartz DE, Rieder J. Pharmacokinetidcs of Sulfamethoxazole + Trimethoprim in Man and Their Distribution in the Rat. Chemotherapy 1970;15:337-355.

Kaplan SA, Weinfeld RE, Abruzzo CW, McFaden K, Jack ML and Weissman L. Pharmacokinetic Profile of Trimethoprim-Sulfamethoxazole in Man. JID 1973;128(Suppl):S547-S555.

Among these studies, only Kaplan, et al. mentions adverse reactions. This study consisted of a 13 week crossover study of 24 male volunteers. The subjects received multidose TMP/SMX 160/800 or TMP-SMX 80/400 and single dose TMP-SMX 400/2000. The single dose arm also administered TMP 400 alone and SMX 2000 alone. Black hairy tongue appeared in two patients receiving the high dose and three subjects given the low dose. Flatulence appeared in three subjects given the high dose and five subjects given the low dose. Bone marrow remained normal in all subjects.

Johnson WA, Chartrand. The Metabolism and Excretion of Phenazopyridine Hydrochloride in Animals and Man. Toxicol Appl Pharmacol 1976;37:371-376.

Thomas BH, Whitehouse LW, Solomonraj G, Paul CJ. Excretion of Phenazopyridine and its Metabolites in the Urine of Humans, Rats, Mice, and Guinea Pigs. J Pharm Sciences 1990;79, No. 4.

Johnson WJ, Burba J. Metabolic Fate of Diaminophenylazopyridine. (Abstract) Fed Proc 1966;25:734.

These studies do not mention adverse events.

***Reviewer's note:*** *The numbers cited are too small to suggest that dose/duration of TMP/SMX are related to toxicity. See pharmacokinetic review for discussion of the pharmacokinetic parameters. The dose that is proposed in the submitted application is that already labeled for UTI.*

**Pharmacokinetic study**:
At the request of DAIDP's Biopharmaceutics Review Division, the Sponsor undertook a small drug interaction study. For a more complete discussion of the study, see the biopharmaceutical review. Here is a brief synopsis:

**Title**: A Randomized, Multiple-Dose, Two-Way Crossover Drug Interaction Study in Healthy Female Subjects

**Objective**: To confirm that the combination of both drugs (TMP/SMX & pyridium) at the dosages proposed in the application does not cause any untoward effects and to determine whether either drug affects the plasma concentration of the other.

**Study Population**: Twelve healthy female subjects, based on medical history, physical examination, clinical laboratory examinations, and electrocardiography.

**Study Design**: The table below summarizes the study design.

| Treatment Regimen | Period 1– Days 1 to 3 | Period 1– days 4 to 6 | Washout period– 9 days | Period 2– days 1 to 3 | Period 2– days 4 to 6 |
|---|---|---|---|---|---|
| Regimen A 6 subjects | Pyridium | Pyridium + TMP/SMX | No therapy | TMP/SMX | Pyridium + TMP/SMX |
| Regimen B 6 subjects | TMP/SMX | Pyridium + TMP/SMX | No therapy | Pyridium | Pyridium + TMP/SMX |

The study prohibited use of any concurrent medications, including over-the-counter medications.

**Drug Administration and Outcome Measures**:
The schedule below is the same for both periods, but the crossover design reassigned those subjects who received Regimen A in Period 1 to Regimen B in Period 2 and reassigned those subjects who received Regimen B in Period 1 to Regimen A in Period 2. Sampling was the same for all subjects, regardless of regimen assigned.

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---|---|---|---|---|---|
| Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>None | Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>None | Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>None | Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm | Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm | Regimen A<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm |
| Regimen B<br>Pyridium:<br>None<br>TMP/SMX:<br>8 am, 5 pm | Regimen B<br>Pyridium:<br>None<br>TMP/SMX:<br>8 am, 5 pm | Regimen B<br>Pyridium:<br>None<br>TMP/SMX:<br>8 am, 5 pm | Regimen B<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm | Regimen B<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm | Regimen B<br>Pyridium:<br>8am, 12 pm, & 5 pm<br>TMP/SMX:<br>8 am, 5 pm |
| 7 am Blood sample for pyridium & TMP/SMX levels | Pooled 24 hour urine collection*:<br>Pyridium & TMP/SMX levels | 6 pm Blood sample for pyridium & TMP/SMX levels | | Pooled 24 hour urine collection:<br>pyridium & TMP/SMX levels | 6 pm Blood sample for pyridium & TMP/SMX levels |

* Collection started on day 2, 34 hours after first dose had been administered and ended on day 3, 58 hours after the first dose had been administered.

Note that the levels drawn on day 3 would be 1 hour post dose for drug, whether TMP/SMX or pyridium. Levels drawn on day 6 would be 1 hour post dose for drug TMP/SMX and pyridium. None of these levels would be a peak level.

"Peak serum levels average approximately 1.75 µg/mL for TMP and 37.5 µg/mL for SMX after a single double-strength tablet is ingested by patients with normal renal function. The peak serum levels of TMP and SMX occur at 1 to 4 hours, respectively."[1]

[1] Gleckman R, Czachor JS. Chapter 25. Trimethoprim-Sulfamethoxazole in Infectious Diseases, 2d ed., eds. Gorbach SL, Bartlett JG, Blacklow NR. WB Saunders Co., 1998, p 270.

See pharmacokinetic review for discussion of study's findings. It appears that levels of SMX, TMP and pyridium are higher than would be expected suggesting a possible drug interaction.

***Reviewer's note:*** *It is a significant design flaw that the sampling was done 1 hour post dose, not at the expected peak. The objective of the study was to determine whether drug interaction occurred. Without a peak level one could not know whether this parameter is affected. However, the single value provided suggests that there is some interaction that elevates drug levels. See biopharm review by Drs. Sun and Pelsor. This review will focus on whether there is a clinical significance to this finding, and, if so, how to label it.*

**Implications of PK Interaction:**

It is believed that shorter therapies of TMP/SMX with lower dosage have less toxicity:

> The most frequent adverse effects of TMP-SMZ are gastrointestinal, including nausea, vomiting, and anorexia, and sensitivity skin reactions in the form of rash and urticaria; each occurring in about 3.5% of patients. The incidence and severity of these effects generally are dose-related.[2]

> Untoward reactions are associated with the administration of TMP-SMX in 6% to 8% of patients who do not have AIDS. Nearly half of the adverse reactions occur within 72 hours after oral administration [citations omitted].[1]

The most frequent adverse events, with the exception of skin rash, are fairly nonspecific. The PK study submitted by the Sponsor contained only 12 patients and is therefore too small to provide any real insight on adverse events. Attached as Appendix 3 are the charts submitted by the Sponsor summarizing laboratory findings, vital signs and adverse events.

**Laboratory Findings:**
With respect to laboratory findings, the combination of TMP/SMX + pyridium versus TMP/SMX alone had statistically significant ($p<0.05$) changes in the following parameters: hemoglobin, WBC, mean corpuscular hemoglobin and concentration, MCV, triglycerides, anion gap, creatinine, BUN/creatinine ratio, calcium, uric acid, total bilirubin, and indirect bilirubin. None of the mean values was outside the normal range. These laboratory changes are consistent with consequences of more extreme laboratory abnormalities reported in the current label for TMP/SMX (agranulocytosis, aplastic anemia, leukopenia, neutropenia, megaloblastic anemia, elevation of serum transaminase and bilirubin, and BUN and serum creatinine elevation).

***Reviewer's note:*** *These findings are consistent with the administration of TMP/SMX. It is possible that the combination of TMP/SMX and pyridium may have a greater effect on these parameters than TMP/SMX alone. However, this is a small study and drawing any conclusions becomes impossible. None of the mean findings strayed from the normal range.*

The combination of TMP/SMX + pyridium versus pyridium alone had statistically significant ($p<0.05$) changes in the following parameters: hemoglobin, WBC, mean corpuscular hemoglobin and concentration, segmented neutrophils, lymphocytes, triglycerides, chloride, anion gap, creatinine, BUN/creatinine ratio, uric acid, total bilirubin, and direct bilirubin. Once again, no mean value fell outside the range of normal values. The 1997 labeling for pyridium is scant with respect to Adverse Reactions. It merely contains this statement with respect to clinical adverse events and laboratory value changes:

> "Headache, rash and occasional gastrointestinal disturbance. An anaphylactoid-like reaction has been described.

---

[2] Lundstrom TS, Sobel JD. "Vancomycin, Trimethoprim-Sulfamethoxazole, and Rifampin" in Infectious Disease Clinics of North America 1995; 9:3 p756

Methemoglobinemia, hemolytic anemia, renal and hepatic toxicity have been described, usually at overdosage levels...."

***Reviewer's note**: The changed values, as described above, are not outside normal parameters and no distribution parameters are provided. Thus, it is difficult to attribute significance to these findings.*

**Changes in Vital Signs**: Vital signs recorded during the study are attached as Appendix 3. There was a statistically but not clinically significant difference in heart rate and respiratory rate when Day 2 Regimen "A" data (mean heart rate 70.83 bpm and mean respiratory rate 17.50 bpm) are compared with Day 5 (mean heart rate 75.74 bpm and mean respiratory rate 16.26 bpm). A statistically but not clinically significant difference in respiratory rate and temperature when Day 2 Regimen "B" data (mean respiratory rate 18.00 bpm and temperature 96.92 F) are compared with Day 5 data (mean respiratory rate 16.26 bpm and temperature 97.56 F).

***Reviewer's note**: These findings are clinically insignificant and of no practical importance.*

**Adverse reactions:**
Thirteen adverse events were reported by six of the 12 patients. See Charts summarizing the Adverse Events and the Sponsor's summary AEs compiled from published clinical trials in Appendix 4. The events the sponsor reports are fairly general and nonspecific: 3 complaints of headache, 2 complaints of constipation, 2 complaints of vomiting, 2 complaints of nausea, and 1 complaint each of pallor, nervousness, eye pain, and pharyngitis. One patient had complaints of nausea, vomiting, headache, pallor and nervousness; she was found to be pregnant when she checked in for study period 2 and was dropped from the study. The eye pain and pharyngitis was deemed unrelated to the study drugs by the investigators. All the other AEs were deemed possibly related to the study drug.

The findings are nonspecific and the numbers very small. It is impossible to determine from the limited scope of this pharmacokinetic study whether the administration of TMP-SMX and pyridium results in more AEs than TMP-SMX alone.

***Reviewer's note**: The AEs are nonspecific and it is certainly not possible to ascribe the events to the TMP-SMX/pyridium combination. However, AEs are fairly common with TMP-SMX therapy. Some of the rare AEs are serious, even life threatening. It is generally believed that the longer the duration of therapy, the greater the risk of AE and the higher the dose of TMP-SMX, the greater the risk of AE (reference cited above and personal communication, W. Stamm). However, there appears to be no information on whether a pharmacokinetic profile suggesting higher drug levels results in more, or more serious, AEs (personal communication, W. Stamm).*

**Compiled Cumulative Safety Data for Trimethoprim-Sulfamethoxazole and Phenazopyridine submitted by Sponsor:**
See Appendix 4 for a table that summarizes most common AEs for TMP/SMX and pyridium drawn from published literature.

***Reviewer's note:** Review of the table confirms that the AEs reported are adequately reflected in the submitted label.*

**Original Labeling submitted by the Sponsor with respect to the Pharmacokinetic study:**
The Sponsor submitted the following label with respect to the study:

**Drug Interaction Study**
In a prospective two-way crossover drug interaction study between sulfamethoxazole/trimethoprim DS and phenazopyridine hydrochloride (200 mg) administered singly [redacted] then in combination [redacted] to 12 healthy female subjects, it was determined that the [redacted] plasma concentrations of trimethoprim.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

**Review of the Adverse Event Reporting Systems (AERS) for toxicity:**
The AERS database at FDA was evaluated for entries of adverse events related to trimethoprim-sulfamethoxazole alone, pyridium alone, and the combination. No denominator information is available to determine rates. Because pyridium is available over the counter and TMP-SMX and pyridium have been available as generic drugs by prescription for years, even marketing information would not be useful in attempting to provide a credible denominator.

No signals related to unique toxicities were discerned. TMP-SMX had about 11,000 entries; pyridium and pyridim + TMP-SMX in combination had far fewer.

***Reviewer's note**: The AERS database cannot provide an answer to the question of whether clinically more adverse events occur when pyridium is taken in combination with TMP-SMX than when TMP-SMX is taken alone. Such an evaluation requires the ability to determine rates. No denominator is available to assess rates. In addition, the voluntary nature of the reporting system further diminishes what might be a reliable measurement. All the drugs being investigated have be marketed for many years (each predating MEDWATCH by at least a decade). Pyridium is also available OTC, and any marketing data about coadministration drawn from marketing data like IMS would be flawed. The postmarketing experience with these drugs has allowed for a complete listing of adverse events in the current label. The label even reflects that there are susceptible populations for adverse events for which greater prescribing caution is required (geriatric, neonates, renal and hepatic dysfunction, etc.) A "signal" is usually a vanishingly rare or unique event that appears in a cluster of association. No such unusual adverse event was detected.*

**Clinical Support submitted by the Sponsor:**
The submission is in the form of a paper" NDA and the Sponsor has submitted support for its application in the form of publications. These are summarized in a bibliography, attached as Appendix 5.

***Reviewer's note**: The above citations provide overwhelming support for the efficacy of the proposed dose of TMP/SMX in the treatment of uncomplicated UTI.*

**Review of Amendment Date May 25, 2000:**
In a May 9, 2000 telecon, the Agency requested that Able Laboratories provide any additional literature that supported the safety of the combination of pyridium and TMP-SMX. The company responded on May 25, 2000 with an Amendment that contained the following information:

(1) Product insert for URO BACTRIM® FORTE, a drug manufactured by Roche Argentina for the treatment of urinary tract infections. Each Uro Bactrim® Forte tablet consists of 160 mg TMP, 800 mg SMX and 200 mg pyridium. It is to be administed one tablet bid for 5 days, which is 3 days longer than the duration proposed for the pyridium component of Zotrim™ UTI therapy.

***Reviewer's note**: The regimen proposed for Uro Bactrim® Forte is different from that of Zotrim™ UTI therapy. Zotrim™ UTI consists of pyridium three times a day for two days and TMP/SMX twice a day for 10 days. A direct comparison is not possible. In addition, the label provides no information on toxicity rates. The adverse events listed in the Uro Bactrim® Forte label include events listed in the TMP/SMX label, pyridium label and proposed Zotrim™ UTI label (skin eruptions, including Stevens-Johnson syndrome, blood dyscrasias, aseptic meningitis, allergic reactions, increased risk of hepatic or renal dysfunction with advanced age). However, the label does not provide any information on rates of adverse events or increased risk of adverse events due to drug interaction.*

Tessler, BK, Oliveira, S. Comparative study of the association of sulfamethoxazole-trimethoprim-phenazopyridine hydrochloride Uro Bactrim® Forte and norfloxacin in the treatment of urinary tract infections. Folha Med., v. 94, 47-49 (1987).

(2) A randomized, double-blind study from Brazil of forty patients with urinary tract infections to evaluate the advantages of the analgesic effect of Uro Bactrim® Forte for 10 days versus norfloxacin for 10 days. There were only twenty patients in each arm and efficacy was equivalent. Fewer complaints of dysuria were recorded in the Uro Bactrim® Forte arm. Adverse events recorded in the Uro Bactrim® Forte arm were one patient with epigastralgia and one patient with nausea. In the norfloxacin arm, there were three patients with epigastralgias, two cases of epigastralgias associated with nausea, and one case of heartburn.

***Reviewer's note**: This trial is inadequate to make any conclusions regarding adverse events, and no laboratory values other than urine culture were reported.*

(3) Information from the world-wide web (Medscape), available drug-drug interaction data, drug-laboratory interaction data, side effects, patient monographs, etc. for TMP, SMX and pyridium as well as for combination therapy, including the combination of TMP, SMX, and pyridium.

***Reviewer's note**: This information provides monographs of the sort physicians or pharmacists would give patients to describe possible side effects. It also includes lists of adverse events. All the adverse events are already labeled. The information does not provide any clarity as to whether the combination of TMP-SMX or pyridium would increase rates of adverse reactions over TMP-SMX or pyridium alone.*

(4) Marketing data from Scott-Levin and IMS which indicate that TMP-SMX DS is prescribed in the United States along with analgesic about 10-11% of the time, and that when so prescribed, pyridium 200 mg USP is the analgesic prescribed 95% of the time. Data on the number of prescriptions of TMP-SMX DS and pyridium are also provided. Approximately [redacted] prescriptions for TMP-SMX are written with a prescription for pyridium.

***Reviewer's note**: This does not reflect over-the-counter use of pyridium. The combination of TMP-SMX with pyridium may be much more common than 11% because because of pyridium's OTC status. The administration of TMP-SMX with pyridium is common in the United States. This information does not provide any indication of whether the combination of TMP-SMX and pyridium results in greater rates of adverse events due to drug interaction than either drug administered alone.*

(5) Data from Mayo Clinic's website on [redacted] which is an FDA-approved combination therapy of SMX and pyridium, with a higher dose (2 grams and 400 mg respectively) than the dosing proposed with the combination drugs in Zotrim™ UTI Therapy.

***Reviewer's note**: This information is a patient monograph describing possible adverse events and other patient information. The events are labeled events. There is no way to determine whether coadministration of SMX and pyridium results in a greater number of adverse events than administration of either drug alone.*

***Reviewer's note**: Review of this amendment provides no information on whether taking TMP-SMX with pyridium would result in more adverse events due to a drug-drug interaction than taking TMP-SMX or pyridium alone. Co-prescription is common in the United States and a previous AERS review could not determine whether coadministration resulted in more toxicity because such an investigation might reveal unique toxicity, but cannot determine rates. Based on the available information, there is no way to assess whether administering TMP-SMX with pyridium would result in a great number of adverse events than administering TMP-SMX alone.*

**Conclusions and Recommendations:**

Currently pyridium is available over the counter, and TMP-SMX is available by prescription. Not only are these drugs prescribed together, but a consumer could easily add pyridium available over the counter to TMP-SMX available by prescription. This proposal represents a convenience rather than an innovation. Efficacy of a 10 day course of TMP/SMX in uncomplicated UTI is proven. Efficacy of pyridium as a urinary analgesic is less assured, but 40 years of use support the claim, and pyridium has monograph status.

The dilemma rests on the pharmacokinetic study that was undertaken by the sponsor at the FDA's request (see pharmacokinetic review). The study supports an interaction between pyridium and TMP-SMX that raises drug levels by up to 60% peak. The clinical consequences of such interaction are unknown, and the concern is that toxicity made be greater. No compelling information is available that directly answers the issue of elevated risk related to increased drug levels for a three day exposure to the combination product in a low risk outpatient population with uncomplicated urinary tract infection. Increased risk of adverse event is attributed to higher doses of TMP-SMX given for longer periods of time, such as the course necessary to treat *Pneumocystis carinii* pneumonia (2 double strength TMP-SMX tablets four times a day for four weeks).

The toxicities of both drugs are adequately described in the label. The label also includes information on special populations more vulnerable to adverse events (for example, neonates, geriatrics, patients with hepatic and renal dysfunction).

The recommendation of this Medical Officer is for approval of the product with the label modified as described in the following section of this review.

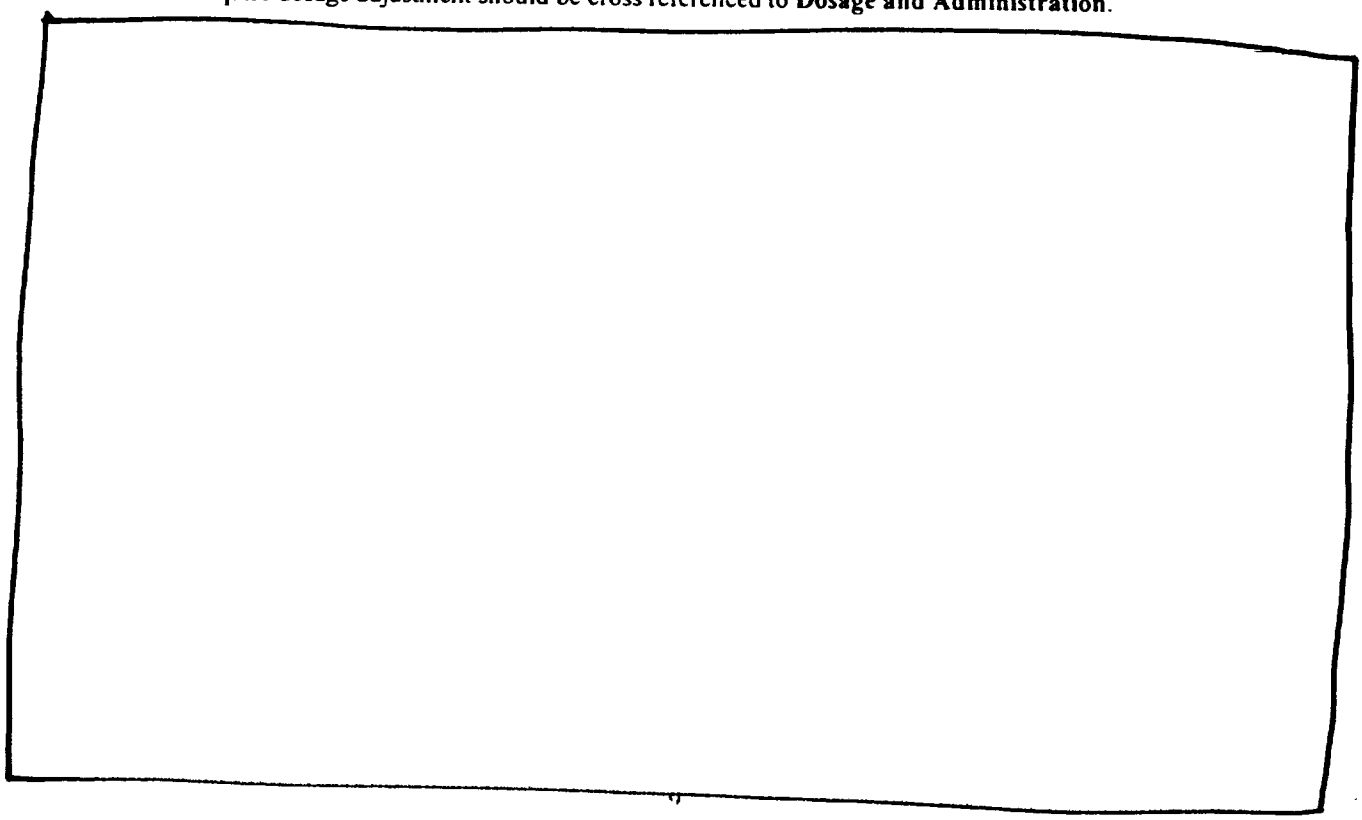
**Recommendations for Final Labeling**:
See marked up final label attached as Appendix 6.

Page 1. Eliminate "The individual products contained in this package should not be used alone or in combination for other purposes. The information described in this labeling concerns only the use of these products as indicated in this combination package."

***Reviewer's note**: The labeling reflects the blister pack. Zotrim UTI™ is labeled only for treatment of uncomplicated urinary tract infection. The above language is implicit in product labeling.*

Page 1 and throughout label: Information for trimethoprim should precede information for sulfamethoxazole throughout label. Information for trimethoprim/sulfamethoxazole should precede information for pyridium throughout label.

Page 2: In the **Clinical Pharmacology** section, the mention that patients with severely impaired renal function require dosage adjustment should be cross referenced to **Dosage and Administration**.



Page 8: Change "**Use in Elderly**" to "**Geriatric Use**".

Page 9: Eliminate the current description of the interaction study. Insert the following:

***Interaction between Trimethoprim/sulfamethoxazole and Phenazopyridine Hydrochloride***
In a prospective two-way crossover drug interaction study between trimethoprim/ sulfamethoxazole DS and phenazopyridine hydrochloride (200 mg) administered first singly, then in combination to 12 healthy female subjects for three days, it was determined that plasma concentrations of trimethoprim, sulfamethoxazole, and phenazopyridine hydrochloride were significantly increased compared to when either drug product was administered alone (see **CLINICAL PHARMACOLOGY** section). Some laboratory values were altered when phenazopyridine hydrochloride was administered concomitantly with trimethoprim/sulfamethoxazole. No values fell outside the normal range. The clinical significance of these changes is unknown.

**CHANGES* IN HEMATOLOGY AND CLINICAL CHEMISTRY PARAMETERS BETWEEN SINGLE TREATMENT TRIMETHOPRIM/SULFAMETHOXAZOLE OR PHENAZOPYRIDINE (TMP/SMX OR PZP) AND COMBINATION TREATMENT TMP/SMX AND PZP (N=12)**

| Parameter | Baseline (mean value) | PZP given alone (mean value) | TMP/SMX alone (mean value) | TMP/SMX and PZP in combination (mean value) | Normal Value |
|---|---|---|---|---|---|
| **HEMATOLOGY** | | | | | |
| Hemoglobin (gm/dL) | | 13. | | | 11.0-15.0 |
| WBC ($x10^3$/dL) | | 8. | | | 4.0-10.0 |
| **CLINICAL CHEMISTRY**** | | | | | |
| Creatinine (mg/dL) | | | | | 0.5-1.4 |
| Total Bilirubin (mg/dL) | | | | | 0.2-1.2 |
| Direct Bilirubin (mg/dL) | | | | | 0.0-0.3 |
| Indirect Bilirubin (mg/dL) | | | | | 0.0-1.1 |

***Reviewer's note:*** *This section above accurately describes the drug interaction study and reports those findings that appear to be valid and reliable. Mention of adverse events have been eliminated because the study is far to small to derive any conclusions regarding adverse events. No conclusions can be drawn regarding the clinical implications and this is stated in the above labeling section.*

/S/

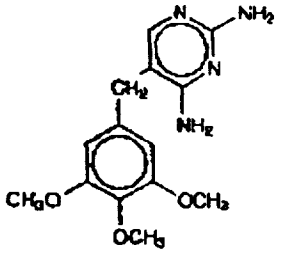
Holli Anne Hamilton, MD, MPH
Medical Officer, HFD-104 , 12/12/00

Concurrence:

J Soreth, MD/ Acting Division Director and Team Leader, HFD-520 /S/ 12/21/00
G Chikami, MD/Division Director, HFD-520 /S/ 12/21/00

cc: Original NDA 21-105
HFD-104
HFD-340
HFD-520
HFD-520/MO/HHamilton
HFD-520/Pharm/KSeethaler
HFD-520/PharmTL/ROsterberg
HFD-520/Micro/HSilver
HFD-520/MicroTL/ASheldon
HFD-520/Chem/BShetty
HFD-520/ChemTL/DKatague
HFD-520/Biopharm/HSun
HFD-520/BiopharmTL/FPelsor
HFD-520/Biostat/DLin
HFD-520/CSO/BDuvall-Miller

# Appendix One



Rx only

THE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED.

For use of the individual components when dispensed as medications outside this combination package for treating urinary tract infections (UTI), please see the package inserts for the individual products.

**DESCRIPTION**

sulfamethoxazole/trimethoprim double strength (800 mg/160 mg) tablets for oral administration.

Molecular weight:

***Inactive Ingredients:***

magnesium stearate, sodium starch glycolate,

sulfamethoxazole bid, the mean steady-state plasma concentration of trimethoprim was 1.72 g/mL. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 g/mL and 68.0 g/mL, respectively. These steady-state levels were achieved after three days of administration[1].

Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as $N_4$-acetylated metabolite.[2] When administered together, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both trimethoprim and sulfamethoxazole distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in breast milk.

***Microbiology:***

Thus, sulfamethoxazole/trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

*In vitro* studies have shown that bacterial resistance develops more slowly with trimethoprim with either trimethoprim or sulfamethoxazole alone.

*In vitro* serial dilution tests have shown that the spectrum of antibacterial activity of sulfamethoxazole/trimethoprim includes the common urinary tract bacterial pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible:

1 page(s) of revised draft labeling has been redacted from this portion of the review.

## INDICATIONS AND USAGE

The components of [redacted] (phenazopyridine hydrochloride/ sulfamethoxazole/trimethoprim) are indicated in the treatment of urinary tract infections as follows:

Phenazopyridine Hydrochloride: Is indicated for the symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of the lower urinary tract mucosa caused by infection. The use of phenazopyridine hydrochloride for relief of symptoms should not delay definitive diagnosis and treatment of causative conditions. Because it provides only symptomatic relief, prompt appropriate treatment of the cause of pain must be instituted and phenazopyridine hydrochloride should be discontinued when symptoms are controlled.

[redacted]

Sulfamethoxazole/Trimethoprim: Is indicated for the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis* and *Proteus vulgaris*. [redacted]

## CONTRAINDICATIONS

This therapy is contraindicated for use in patients with a known hypersensitivity to phenazopyridine hydrochloride, trimethoprim or sulfonamides and in those with renal insufficiency or documented megaloblastic anemia due to folate deficiency. Sulfamethoxazole/Trimethoprim is also contraindicated in pregnant patients at term and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Sulfamethoxazole/Trimethoprim is contraindicated in pediatric patients less than two months of age.

## WARNINGS

**FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS. SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS TRIMETHOPRIM/SULFAMETHOXAZOLE, SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION.** In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders (see PRECAUTIONS section).

Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura, or jaundice may be early indications of serious reactions.

**Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.** The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including trimethoprim/sulfamethoxazole, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug

discontinuation alone. In moderate to severe cases, consideration should be give to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *C. difficile.*

## PRECAUTIONS

### *General*

Phenazopyridine Hydrochloride: A yellowish tinge of the skin or sclera may indicate accumulation due to impaired renal excretion and the need to discontinue therapy. The decline in renal function associated with advanced age should be kept in mind.

Sulfamethoxazole/Trimethoprim: Sulfamethoxazole/Trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states), and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections).

The use of sulfamethoxazole/trimethoprim by elderly patients may increase the risk of severe adverse reactions, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions or generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS sections) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION section).

### *Information for Patients*

Phenazopyridine Hydrochloride produces an orange to red color in the urine and may stain fabric. Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation. Staining of contact lenses has been reported.

[redacted] is a white capsule-shaped scored tablet with beveled edges, plain on one side, scored in half on the other, with "93" embossed on one side of the breakline and "089" embossed on the other side. [redacted]

### *Laboratory Tests*

Appropriate culture and susceptibility studies should be performed before and throughout treatment in patients receiving sulfamethoxazole/trimethoprim. Complete blood counts should be

done frequently; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole/trimethoprim should be discontinued. Urinalysis with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

***Drug Interactions***

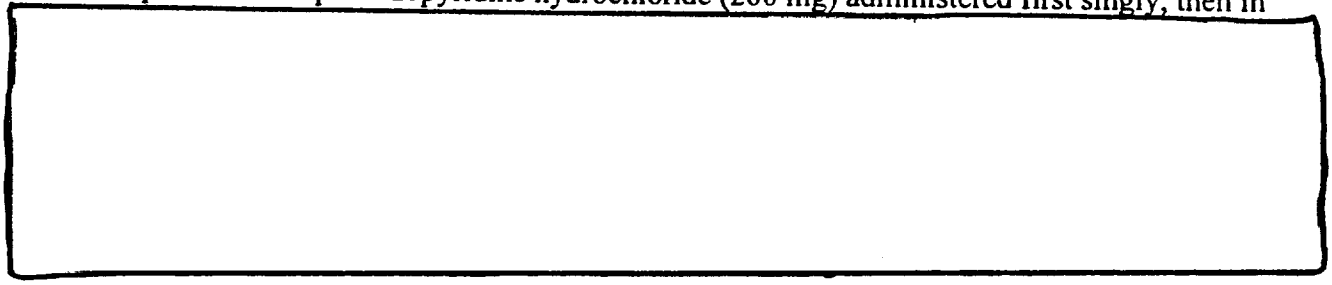
In elderly patients concurrently receiving sulfamethoxazole/trimethoprim and certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. It has been reported that sulfamethoxazole/trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole/trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole/trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole/trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

***Interaction between Sulfamethoxazole/Trimethoprim and Phenazopyridine Hydrochloride***

In a prospective two-way crossover drug interaction study between sulfamethoxazole/ trimethoprim DS and phenazopyridine hydrochloride (200 mg) administered first singly, then in



***Drug/Laboratory Test Interactions***

Due to its properties as an azo dye, phenazopyridine hydrochloride may interfere with urinalysis based on spectrometry or color reactions.

Sulfamethoxazole/Trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimation of about 10% in the range of normal values.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Sulfamethoxazole/Trimethoprim:

*Carcinogenesis:* Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole/trimethoprim.

*Mutagenesis:* Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1000 times human plasma levels in these same cells, a low level of chromosomal damage was induced at one of the laboratories. No chromosomal abnormalities were observed in cultured human leukocytes at concentrations of trimethoprim up to 20 times human steady-state plasma levels. No chromosomal effects were detected in peripheral lymphocytes of human subjects receiving 320 mg of trimethoprim in combination with up to 1600 mg of sulfamethoxazole per day for as long as 112 weeks.

*Impairment of Fertility:* No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

***Pregnancy***

Sulfamethoxazole/Trimethoprim: Teratogenic Effects: Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed

in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead, resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursells[5], in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, sulfamethoxazole/trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nonteratogenic Effects:* See CONTRAINDICATIONS section.

***Nursing Mothers***

No information is available on the appearance of phenazopyridine hydrochloride or its metabolites in human milk. (See CONTRAINDICATIONS section.)

***Pediatric Use***

[redacted] is not recommended for pediatric patients [redacted] (see INDICATIONS AND USAGE and CONTRAINDICATIONS sections).

**ADVERSE REACTIONS**

Phenazopyridine Hydrochloride: Headache, rash and occasional gastrointestinal disturbance. An anaphylactoid-like reaction has been described.

Methemoglobinemia, hemolytic anemia, renal and hepatic toxicity have been described, usually at overdosage levels (see OVERDOSAGE section).

Sulfamethoxazole/Trimethoprim: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT** (see WARNINGS section).

*Hematologic:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

*Allergic:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schonlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa, and systemic lupus erythematosus have been reported.

*Gastrointestinal:* Hepatitis, including cholestatic jaundice and hepatic necrosis, elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

*Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

*Metabolic:* Hyperkalemia, hyponatremia.

*Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

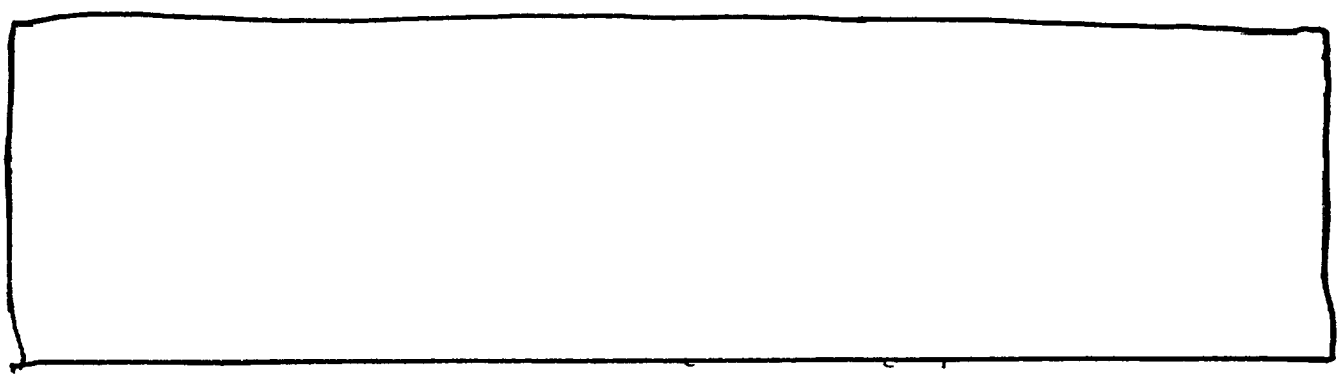
*Psychiatric:* Hallucinations, depression, apathy, nervousness.

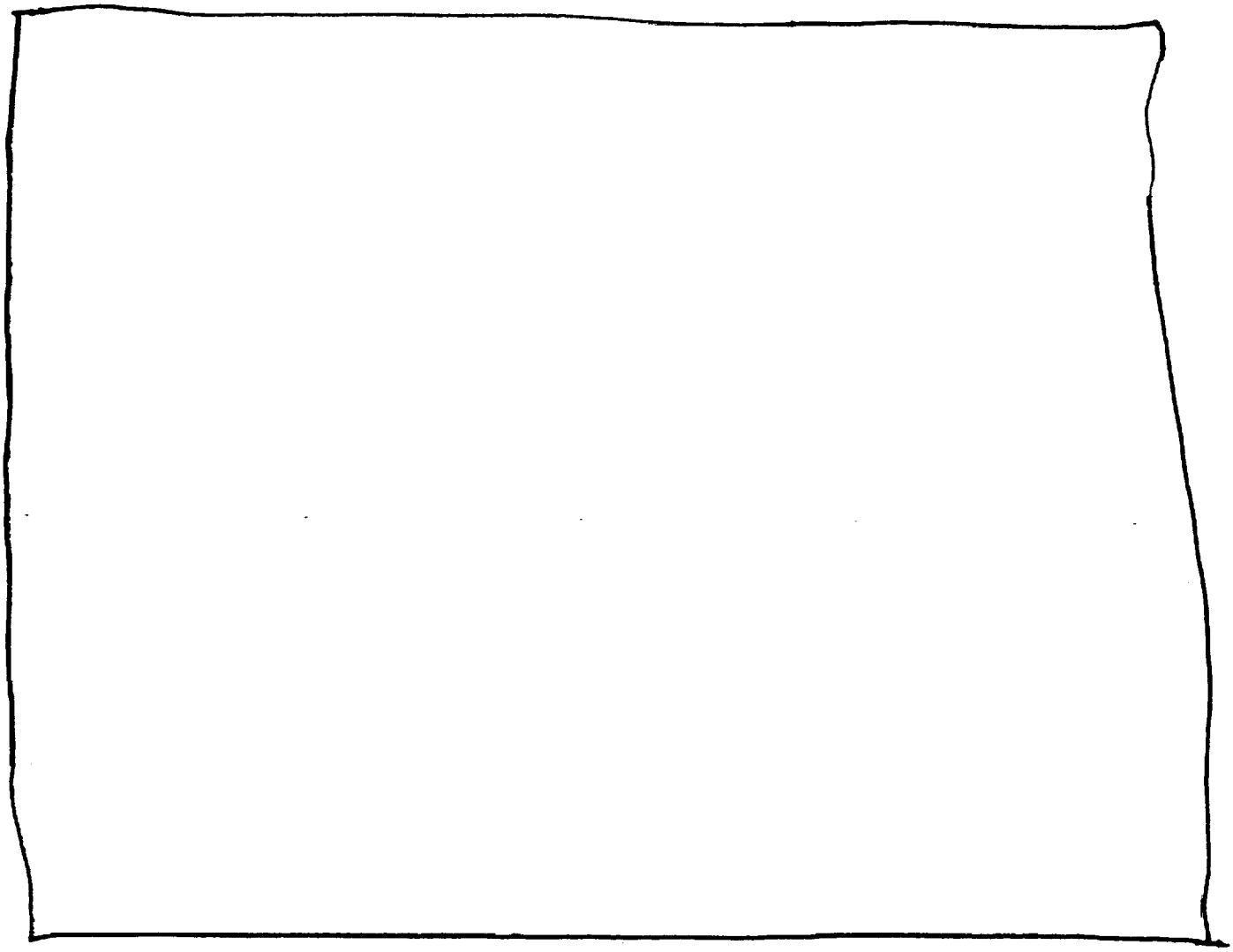
*Endocrine:* The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

*Musculoskeletal:* Arthralgia and myalgia.

*Respiratory System:* Cough, shortness of breath, and pulmonary infiltrates (see WARNINGS section).

*Miscellaneous:* Weakness, fatigue, insomnia.





**OVERDOSAGE**

In case of an overdose of [redacted] patients should contact a physician, poison control center, or emergency room.

Phenazopyridine Hydrochloride: Exceeding the recommended dose in patients with good renal function or administering the usual dose to patients with impaired renal function (common in elderly patients) may lead to increased serum [redacted] and toxic reactions. Methemoglobinemia generally follows a massive, acute overdose. Methylene blue 1 to 2 mg/kg body weight intravenously or ascorbic acid 100 to 200 mg give orally should cause prompt reduction of the methemoglobinemia and disappearance of the cyanosis which is an aid in diagnosis. Oxidative Heinz body hemolytic anemia may also occur, and "bite cells" (degmacytes) may be present in a chronic overdosage situation. Red blood cell G-6-PD deficiency may predispose to hemolysis. Renal and hepatic impairment and occasional failure, usually due to hypersensitivity, may also occur.

Sulfamethoxazole/Trimethoprim: *Acute*: The amount of a single dose of sulfamethoxazole/trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness, and unconsciousness. Pyrexia, hematuria, and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion, and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim.

The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

*Chronic:* Use of sulfamethoxazole/trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

## DOSAGE AND ADMINISTRATION

***Adults***

Phenazopyridine Hydrochloride: One (1) 200 mg tablet 3 times a day after meals. The administration of phenazopyridine hydrochloride should not exceed 2 days.

Sulfamethoxazole/Trimethoprim: One (1) double strength (800 mg/160 mg) tablet every 12 hours for 10 days.

## HOW SUPPLIED

Store at controlled room temperature 15°C-25°C (59°F-77°F) in a dry place and protected from light.

**REFERENCES**


5. Brumfitt W, Pursell R. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women. *J Infect Dis.* November 1973;128 (suppl):5657-5663.


Phenazopyridine Hydrochloride 200 mg tablets are manufactured by:
Able Laboratories, Inc.
6 Hollywood Court,
South Plainfield, NJ 07080

Sulfamethoxazole/Trimethoprim double strength tablets are manufactured by:

is packaged by:
Packaging Coordinators, Inc.
3001 Red Lion Road
Philadelphia, PA 19114
for Able Laboratories, Inc.

# Appendix Two

Alano, F.A., Jr., and Webster, G.D., Jr.: *Acute Renal Failure and Pigmentation Due to Phenazopyridine.* Annals of Int. Med., 72: 89-91 (1970)

American Conference of Governmental Industrial Hygienists.: *Documentation of the Threshold Limit Values for Substances in Workroom Air.* (H.B. Elkins, ed.), 3rd Ed. American Conference of Governmental Hygienists, Cincinnati, Ohio (1972)

Badley, B.W.: *Phenazopyridine-Induced Hepatitis.* Brit. Med. J., 2: 850 (1976)

Becker, B.A. and Swift, J.G.: *Effective Reduction of the Acute Toxicity of Certain Pharmacologic Agents by Use of Synthetic Ion Exchange Resins.* Toxicol. Appl. Pharmacol.., 1: 42-54 (1959)

Belfield, W.T. and Rolnick, H.C.: *Observations on Physiology and Therapy of Seminal Duct.* J.A.M.A., 89: 2106 (1927)

Bloch, A. and Porter, B.: *Phenazopyridine Poisoning.* Am J. Dis. Child., 117: 369 (1969)

Böhni, E.:Vergleichende *Bakteriologische Untersuchungen mit der Kombination Trimethoprim/Sulfamethoxazole in vitro und in vivo.* Chemotherapy 14 (Suppl.): 1 (1969a)

Böhni, E.:Vergleichende *Chemotherapeutic Activity of the Combination of Tromethoprim and Sulfamethoxazole in Infections of Mice.* Postgrad. Med. J. 45 (Suppl.):18 (1969b)

Braitberg, L.D.: *Variation of Organized Sediment Following Pyridium Administration in Urinary Infections.* J. Lab. & Clin. Med.. 26: 1768-1773 (1941)

Bray, H.G., Clowes, R.C., and Thorpe, W.V.: *The Metabolism of Azobenzene and p-Hydroxyazobenzene in the rabbit.* Biochem. J., 49: LXV (1951)

Brodie, B.B. and Axelrod, J.J.: *The Estimation of Acetanilide and its Metabolic Products, N-acetyl-p-aminophenol and p-aminophenol (free and conjugated) in Biological Fluids and Tissues.* J. Pharmacol. Exp. Ther. 94: 22-28 (1948a)

Brodie, B.B. and Axelrod, J.J.: *The Fate of Acetanilide in Man.* J. Pharmacol. Exp. Ther. 94: 29-38 (1948b)

Brown, T.K.: *Bacteriological Study of Urinary Infection in Pregnancy and Puerperium with Special Reference to Use of Urinary Antiseptic.* South. Med. J., 26: 788-802 (1933)

Brumfitt, W., Eilers, M.C., Pursell, R.L., Reeves, D.S., and Turnbull, A.R.: *Bacteriological Pharmacological and Clinical Studies with Trimethoprim Sulfonamide Combinations.* Postgrad. Med. J. 45 (Suppl.): 56 (1969)

Brumfitt, W. and Pursell, R.: *Double-blind Trial to Compare Ampicillin, Cephalexin, Co-trimoxazole, and Trimethoprim in Treatment of Urinary Infection.* Brit. Med. J., **2**: 673-676 (1972)

Brumfitt, W. and Pursell, R.: *Trimethoprim-Sulfamethoxazole in the Treatment of Bacteriuria in Women.* J. Infect. Dis., **128**(suppl): S657-S663 (1973)

Bruno, G.A. and Christian, J.E.: *Determination of Carbon -14 in Aqueous Bicarbonate Solutions by Liquid Scintillation Counting Techniques. Application to Biological Fluids.* Analyt. Chem. **33**: 1216-1218 (1961)

Burba, J.V.: *The Metabolism and Toxicity of 2,3,6-Triaminopyridine, a Metabolite of Pyridium.* Can. J. Biochem., **45**: 773-780 (1967)

Bushby, S.R.M. and Hitchings, G.H.: *Trimethoprim, a Sulfonamide Potentiator.* Brit. J. Pharmacol. Chemother., **33**: 72-90 (1968)

Cartwright, K. A., Stanbridge, T. N., and Cooper, J.: *Comparison of Once Daily Trimethoprim and Standard Co-trimoxazole in Urinary Infections.* The Practitioner, **226**: 152-156 (1982)

Chakraborty, T. K., R. J. A. Filshie, and Lee, M. R.: *Methaemoglobinemia Produced by Phenazopyridine (Pyridium) in a Man with Chronic Obstructive Airways Disease.* Scot. Med. J., **32**: 185-186 (1987)

Cohen, B.L. and Bovasso, G.J.: *Acquired Methemoglobenemia and Hemolytic Anemia Following Excessive Pyridium (Phenazopyridine Hydrochloride) Ingestion.* Clin. Pediat., **10**: 537-540 (1971)

Compendium of Pharmaceuticals and Specialities. (G.N. Rotenberg, ed.). 9th Ed., p.610. The Canadian Pharmaceutical Assoc., Toronto (1974)

Council on Pharmacy and Chemistry (American Medical Association): *New and Nonofficial Remedies; Pyridium Omitted.* J.A.M.A., **101, No 27**: 2118-2121 (1932)

Counts, G. W., Stamm, W. E., McKevitt, M., Running, K., Holmes, K. K., and Turck, M. *Treatment of Cystitis in Women with A Single Dose of Trimethoprim-Sulfamethoxazole.* Rev. Inf. Dis., **4**: 484-490 (1982)

Cramer, J. A., Mattson, R. H., Prevey, M. L., Scheyer, R. D., and Ouellette, V. L.: *How Often is Medication Taken as Prescribed? A Novel Assessment Technique.* J.A.M.A. **261** (2337-2340 (1989)

Crawford, S.L., Moon, A.E., Jr., Panos, T.C., and Hooks, C.A.: *Methemoglobinemia Associated with Pyridium Administration: Report of a Case.* J Am Med Assoc **146**: 24-25 (1951)

Crawford, E.D. and Mulvaney, W.P.: *Rapid Increase in Calculous Size: A Possible Hazard of Phenazopyridine Hydrochloride Therapy in the Presence of Already Formed Stones.* J. of Urol., **119**: 280-281 (1978)

Cutler, S.J. and Ederer, F.: *Maximum Utilization of the Life Table in Analyzing Survival.* J. Chron. Dis. **8**: 699-712 (1958)

Daschner, F. And Marget, W.: *Treatment of Recurrent Urinary Tract Infection in Children.* Acta Paediatr. Scand., **64**: 105 (1975)

Eisinger A. J., and Jones, R.: *Phenazopyridine Hydrochloride Hemolysis.* Lancet, 151, (1969)

Eybel, C. E., Armbruster, K. F. W., and Ing, T. S.: *Skin Pigmentation and Acute Renal Failure in a Patient Receiving Phenazopyridine Therapy.* J.A.M.A, **228**: 1027-1928, (1974)

Fair, W. R., Crane, D. B., Peterson, L. J., Dahmer, C., Tague, B., and Amos, W.: *Three-day Treatment of Urinary Tract Infections.* J. Urol., **123**: 717-721 (1980)

Feinfeld, D.A., Ranieri, R., Lipner, H.I., and Avram, M.M.: *Renal Failure in Phenazopyridine Overdose.* J.A.M.A., **240**: 2661 (1978)

Fihn, S.D., Johnson, C., Roberts, P.L., Running, K., and Stamm, W.E.: *Trimethoprim-Sulfamethoxazole for Acute Dysuria in Women: A Single-Dose or 10-Day Course: A Double-Blind, Randomized Trial.* Ann. Intern. Med., **108**: 350-357 (1988)

Fincher, M. E., and Campbell, H. T.: *Methemoglobinemia and Hemolytic Anemia after Phenazopyridine Hydrochloride (Pyridium) Administration in End-Stage Renal Disease.* Southern Med. J. **82**: 372-374, (1989)

Fouts, J.R., Kamm, J.J., and Brodie, B.B.: *Enzymatic Reduction of Prontosil and Other Azo Dyes.* J. Pharmacol. Exp. Ther., **120**: 291-300 (1957)

Friedman, G.D. & Ury, H.K.: *Initial Screening for Carcinogenicity of Commonly Used Drugs.* J. Natnl Cancer Inst., **65**: 723-733 (1980)

Gabor, E.P., Lowenstein, L., and deLeeuw, N.K.M.: *Hemolytic Anemia Induced by Phenylazo-diamino-pyridine (Pyridium®).* Can. Med. Assoc. J., **91**: 756-759 (1964)

Galun, E., Oren, R., Glikson, M., Friedlander, M., and Heyman, A: *Phenazopyridine-induced Hemolytic Anemia in G-6-PD Deficiency.* Drug Intell. Clin. Pharm., 21: 994-997 (1987)

Gleckman, R. A: *Trimethoprim-Sulfamethoxazole vs Ampicillin in Chronic Urinary Tract Infections: a Double-blind Multicenter Cooperative Controlled Study.* JAMA, 233: 427-431 (1975)

Goldfinger, S.E. and Marx, S.: *Hypersensitivity Hepatitis Due to Phenazopyridine Hydrochloride.* New Engl. J. Med., **286, No. 20**: 1090-1091 (1972)

Gossius, G., and Vorland, L.: *A Randomized Comparison of Single-dose vs. Three-day and Ten-day Therapy with Trimethoprim-Sulfamethoxazole for Acute Cystitis in Women.* Scand. J. Infect. Dis., **16**: 373-379 (1984)

Greenberg, R.N., Reilly, P.M., Luppen, K.L., Weinandt, W.J., Ellington, L.L., and Bollinger, M.R.: *Randomized Study of Single-Dose, Three-Day, and Seven-Day Treatment of Cystitis in Women.* J. Infect. Dis., **153** (2): 277-282 (1986)

Greenberg, M. S.: *Heinz Body Hemolytic Anemia "Bite Cells" - A Clue to Diagnosis.* Arch. Intern. Med., **136**: 153-155 (1976)

Greenberg, M.S. and Wong, H.: *Methemoglobinemia and Heinz-body Hemolytic Anemia due to Phenazopyridine Hydrochloride.* New Eng. J. Med., **271**: 431-435 (1964).

Gregus, Z., and Klassen, C.D.: Toxicol. Appl. Pharmacol., **63**: 13-20 (1982)

Gruneberg, R.N. and DeLorenzo, W.F.: *Potentiation of Sulfonamides and Antibiotics by Trimethoprim.* Antimicrob. Agents Chemother., **1965**: 430-433 (1966)

Gruneberg, R.N. and Kolbe, R.: *Trimethoprim in the Treatment of Urinary Infections in Hospital.* Brit. Med. J. **1**: 545-547 (1969)

Hirom, P.C., Millburn, P., Smith, R.L., and Williams, R.T.: Biochem. J., **129**: 1071-1077 (1972)

Hitchings, G.H.: *A Biochemical Approach to Chemotherapy.* Ann. N.Y. Acad. Sci., **23**: 700-708 (1961).

Hitchings, G.H.: *Mechanism of Action of Trimethoprim-Sulfamethoxazole.* J. Infect. Dis. **128** (Suppl.): S433-S436 (1973).

Hood, J.W. and Toth, W.N.: *Jaundice Caused by Phenazopyridine Hydrochloride.* J. Amer Med Assoc., **198**: 1366-1367 (1966)

Hooton, T.M., Johnson, C., Winter, C., Kuwamura, L., Rogers, M.E., Roberts, P.L., and Stamm, W.E.: *Single-Dose and Three-day Regimens of Ofloxacin versus Trimethoprim-Sulfamethoxazole for Acute Cystitis in Women.* Antimicrob. Agents Chemother. 35(7): 1479-1483 (1991).

IARC (*International Agency for Research against Cancer*) *Monograph for Evaluating Carcinogenic Risk of Chemicals in Humans - Phenazopyridine and Phenazopyridine Hydrochloride.* IARC V.24 (1980); IARC S.4 (1982), NCI 99 (1978), IARC S.7 (1987)

Iravani, A., Richard, G.A., and Baci, H. *Treatment of Uncomplicated Urinary Tract*

*Infection with Trimethoprim versus Sulfisoxazole with Special Reference to Antibody-Coated Bacteria and Faecal Flora.* Antimicrob. Agents Chemother., **19**: 842-50 (1981a)

Iravani, A., Richard, G.A., Baer, H., and Fennel, R.: *Comparative Efficacy and Safety of Nalidixic Acid versus Trimethoprim/Sulfamethoxazole in Treatment of Acute Urinary Tract Infections in College-Age Women.* Antimicrob. Agents Chemother., **19**(4): 598-604 (1981b)

Johnson, W.J. and Burba, J.: *Metabolic Fate of Diaminophenylazopyridine.* Fed. Proc., **25**: 734 (1966)

Johnson, W.J. and Chartrand, A.: *The Metabolism and Execretion of Phenazopyridine Hydrochloride in Animals and Man.* Toxicol. Appl. Pharmacol., **37**: 371-376 (1976)

Johnson, J.R. and Stamm, W.E.: *Diagnosis and Treatment of Acute Urinary Tract Infections* Infect. Dis. Clin. North Am. **1**: 773 (1987)

Jones, R.H.: *Single-Dose and Seven-day Trimethoprim and Co-trimoxazole in the Treatment of Urinary Tract Infection.* J. Royal Coll.of Ge. Pract. **33**: 585-589 (1983)

Kalberer, F. and Rutschmann, J.: *Eine Schnellmethode zur Bestimmung von Tritium, Radiokohlenstoff und Radioschwefel in Beliebgem Organischem Probenmaterial mittels des Flüssigkeits-Scintillations-Zählers.* Helv. Chim. Acta **44**:1956-1966 (1961)

Kalowski, S., Nanra, R., Mathew, T.H., and Kinkaid-Smith, P.: *Deterioration in Renal Function in Association with Co-Trimoxazole Therapy.* Lancet, **2**: 394-397 (1973)

Kaplan, S.A., Weinfeld, R.E., and Abruzzo, C.W.: *Biological Availability and Biological Equivalence.* Adv. In Automated Analyses **2**: 405-411 (1970a)

Kaplan, S.A., Weinfeld, R.E., Cotler, S., Abruzzo, C.W., and Alexander, K.: *Pharmacokinetic Profile of Trimethoprim in Dog and Man.* J. Pharm. Sci. **59**: 358-363 (1970b)

Kaplan, S.A., Weinfeld, R.E., Abruzzo, C.W., McFaden, K., Jack, M.L., and Weissman, L.: *Pharmacokinetic Profile of Trimethoprim-Sulfamethoxazole in Man.* J. Infect. Dis. **128** (Suppl.): S547-S555 (1973)

Kirwin T.J. Lowsley OS, Menning J.: *The Effects of Pyridium in Certain Urogenital Infections* Am. J. Surg., **62**: 330-335 (1943)

Kornowski, R., Averbuch, M., Jaffe, A., Schwartz, D., and Levo, Y. *School Investig Haematol* 120: 324-325 (1991)

Kremers, P., Duvivier, J., and Heusghem, C.: *Pharmacokinetic Studies of Co-Trimoxazole in Man: III. - Single and Repeated Doses.* J. Clin. Pharmacol. **14**: 112-11[illegible] (1974)

Kronberger, L.: *Testing Stomach Acidity with a Colour Reaction in Urine.* Wien. Med. Wochschr. **111**: 698-700 (1961)

Kuperberg, J., Smith, D., and Vogt, E.: *All in One: The User-Friendly $R_x$ Product.* Pharmaceutical Executive, April (1990)

Leibovici, L., Laor, A., Alpert, G., and Kalter-Leibovici, O.: *Single-dose Treatment of Urinary Tract Infection in Young Women: Data Indicating a High Rate of Recurrent Infection During a Short Follow-up.* Israel J. Med. Sci., 20 257-259 (1984)

Leibovici, L., and Wysenbeek, A.J.: *Single-dose Antibiotic Treatment for Symptomatic Urinary Tract Infections in Women: a Meta-analysis of Randomized Trials.* Qtrly J. Med.,News Series **78**, No. 285: 43-57 (1991)

Linkewich, J.A., Catalano, R.B., and Flack, H.L.: *The Effect of Packaging and Instruction on Outpatient Compliance with Medication Regimens.* Drug Intell. Clin. Pharm., **8**: 10-15 (1974)

Mason, L.M.: *Pyridium Therapy in Genito-Urinary Diseases.* Va. Med. Monthly, **58**: 190-194 (1931)

Mandell and Sande. *Antimicrobial Agents (Continued) Sulfonamides. Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for UTIs.* Chapter 45 in Goodman and Gilman p1047-1064 (1991)

Masterton, R.G. and Bochsler, J.A.: *High-dosage Co-amoxiclav in a Single Dose versus 7 Days of Co-trimoxazole as Treatment of Uncomplicated Lower Urinary Tract Infection in Women.* J. Antimicrob. Chemother. **35**: 129-137 (1995)

McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C., and Caspary, J.: *Responses of the L5178Y Mouse Lymphoma Cell Forward Mutation Assay. V: 27 Coded Chemicals.* Environ. Molecular Mutagenesis, **17**: 196-219 (1991)

Millburn, P.: In *The Hepatobiliary System: Fundamental and Pathological Mechanisms.* Taylor, W., Ed.; Plenum, New York, pp 109-142 (1976)

Morrissey, J.H. and Spinelli, A.N.: *An Experimental Study of the Anesthetic and Analgesic Properties of Pyridium.* J. Urol., **44**: 381-385 (1940)

Mueller, G.C. and Miller, J.A.: *The Reductive Cleavage of 4-Dimethyl-aminoazobenzene by Rat Liver.* J. Biol. Chem., **185**: 145-161 (1950)

Mulvaney, W.P., Beck, C., Brown, R.R.: *Urinary Phenazopyridine Stones.* J.A.M.A., 221 No. 13, 1511-1512 (1972)

Nathan, D.M., Seigal, A.J., and Bunn, H.F.: *Acute Methemoglobinemia and Hemolytic Anemia with Phenazopyridine.* Arch. Int. Med., **137**: 1636-1638 (1977)

National Cancer Institute: *Bioassay of Phenazopyridine Hydrochloride for Possible Carcinogenicity (Tech. Rep. Ser. No. 99).* Department of Health, Education, & Welfare Publication No. (NIH) 78-1349, Washington, D.C. U.S. Government Printing Office (1978)

Newbould, B.B. and Kilpatrick, R.: *Long-acting Sulfonamides and Protein Binding.* Lancet **1**: 887-891 (1960)

Nichols, W.K.: *Anti-Infectives,* In: Remington: The Science and Practice of Pharmacy, 19th ed., Easton, PA, Mack Publishing Company (1995)

Noonan, H. M., Kimbrell, M., Johnson, W. B., and Reuler, J. B.: *Phenazopyridine-induced Hemolytic Anemia.* Urol., **21**: 623-624 (1983)

Norrby, S.R.: *Short Term Treatment of Uncomplicated Lower Urinary Tract Infections in Women.* Rev. Infect. Dis., **12**: 458-467 (1990)

Osol, A. and Pratt, R.: *The United States Dispensatory, 27th Edition, Philadelphia: J.B. Lippincott.* pp. 892-893 (1973)

Pelton, S.I., Shurin, P.A., Klein, J.O., and Finland, M.: *Quantitaive Inhibition of Haemophilus influenzae by Trimethoprim-Sulfamethoxazole.* Antimicrob. Agents Chemother., **12**: 649-654 (1977)

Philbrick, J.T., and Bracikowski, J.P.: *Single-dose Antibiotic Treatment for Uncomplicated Urinary Tract Infections: Less for Less?* Arch. Int. Med., **145**: 1672-1678 (1985)

Physicians' Desk Reference, 1997

Physicians' Desk Reference, 1998

Ponte, C.D., Lewis, M.J., Rogers, J.S., II: *Heinz-Body Hemolytic Anemia Associated with Phenazopyridine and Sulfonamide.* DICP, The Annals of Pharmacotherapy, **23**: 140-2 (1989)

Portwich, F., Büttner, M., and Engelhardt, K.: *Nierenausscheidung und Eiweissbindung von Sulfonamiden.* Klin. Wschr. **41**: 441-451 (1963)

Portwich, F.: *Untersuchung des Mechanismus der Nierenausscheidung von Arzneimitteln.* Antibiot. Chemother., N.Y. **12**: 31[illegible] (1964)

Randazzo, G.P., Ford, E.A., and Glauser, F.L.: *Methemoglobinemia caused by Acute Overdosage of Phenazopyridine.* West. J. Med., **122**: 427-429 (1975)

Ravich, A. and Blaustein, L.: *Study of 100 Suprapubic Prostatectomies.* Long Lsland Med. J., **24**: 425-429 (1930)

Reeves, D. S., Faiers, M. C., Pursell, R. E., and Brumfitt, W.: *Trimethoprim-sulfamethoxazole: Comparative Study in Urinary Infection in Hospital.* Brit. Med. J., **1**: 541-544 (1969)

Remington: *The Science and Practice of Pharmacy.* Nineteenth Edition, Mack Publishing Company (1995)

Reynolds, J.S., Wilkey, J.L., and Choy, J.K.L.: *Clinical Application and Results of Pyridium Therapy.* Illinois Med . J., **78**: 544-547 (1940)

Rieder, J.: *Quantitative Determination of the Bacteriostatic Active Fraction of Sulfonamides and the Sum of their Inactive Metabolites in Body Fluids.* Chemotherapy **17**: 1 (1972)

Rieder, J.: *Physikalisch-chemische und Biologische Untersuchungen an Sulfonamiden. 3. Mitteilung: Beziehungenzwischen einigen Physikalisch-Chemischen Eigenschaftes von Sulfonamiden und deren Schicksal im Menschlichen und Tierischen Körper.* Arzneimittel-Forsch. **13**: 81-88, 95-103 (1963)

Rosen, P.J., Johnson, C., McGehee, W.G., and Beutler, E.: *Failure of Methylene Blue Treatment in Toxic Methemoglobinemia. Association with Glucose-6-Phosphate Dehydrogenase Deficiency.* Ann. Int. Med., **75**: 83-86 (1971)

Rowland, I.R.: Biochem. Pharmacol., **35**: 27-32 (1986)

Rudd, P.: *Medication Packaging: Simple Solutions to Nonadherence Problems ?* Clin. Pharm. Ther., **25**: 257 (1979)

Sand, R.E. and Edelmann, C.M., Jr.: *Pyridium®-Induced Methemoglobinemia. Report of a Case.* J. Pediat., **58**: 845-848 (1961)

Schultz, H.J. and McCaffrey, L.A.: *Acute Cystitis: A Prospective Study of Laboratory Tests and Duration of Therapy.* Mayo Clin. Proc., **59**: 391-397 (1984)

Schwartz, D.E., Koechlin, B.A., and Weinfeld, R.E.: *Spectrofluorometric Method for the Determination of Trimethoprim in Body Fluids.* Chemotherapy **14** (Suppl.): 22 (1969)

Schwartz, D.E. and Rieder, J.: *Pharmacokinetics of Sulfamethoxazole + Trimethoprim in Man and Their Distribution in the Rat.* Chemotherapy **15**: 337-355 (1970)

Schwartz, D.E. and Ziegler, W.H.: *Assay and Pharmacokinetics of Trimethoprim in Man and Animals.* Postgrad. Med. J. **45**: 37-37 (1969)

Shouval, D., Ligumsky, M., and Ben-Ishay, D.: *Effect of Co-Trimoxazole on Normal Creatinine Clearance.* Lancet, **2**: 244-245 (1978)

Smith, D.D., Bell, S.M., Levey, J.M., and Loy, Y.T.: *The Action of Trimethoprim-Sulphamethoxazole Against Urinary Pathogens.* Med. J. Aust. **1**: 263-265 (1972)

Smith, D.: *Compliance Packaging: A Patient Education Tool.* American Pharmacy, **NS29(2)** (1989)

Smith, M.: *The Cost of Non-Compliance and the Capacity of Improved Health care Costs. N&I Pharmaceutical Council; Improving medication Compliance.* Proceedings of a Symposium (1984)

Spinelli, A.N., Keshin, J.G., and Davis, J.E.: *A New Medication for Relief of Urinary Symptoms: A Preliminary Report.* J. Amer. Geriat. Soc., **12**: 771-775 (1964)

Stewart, R. B., and Cluff, L. E.: *A Review of Medication Errors and Compliance in Ambulant Patients.* Clin. Pharm. Ther., **13**: 463-468 (1972)

Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K. and Gori, G.B.: *Test for Carcinogenicity of Food Additives and Chemotherapeutic Agents by the Pulmonary Tumor Response in Strain A Mice.* Cancer Res., **13**: 3069-3085 (1973).

Symposium (Various authors.): *The Synergy of Trimethoprim and Sulfonamides.* Postgrad. Med. J., **45**: Suppl., 3-104 (1969)

Symposium (Various authors.): *The Synergy of Trimethoprim-Sulfamethoxazole.* J. Infect. Dis., **128**: Suppl., 425-816 (1973)

Terrell, J. R.,Spruill, W. J., and Parish, R. C.: *Phenazopyridine-induced Methemoglobinemia,* Drug Intell. Clin. Pharm., **22**: 915 (1988)

Thomas, B.H., Whitehouse, L.W., Solomonraj, G., and Paul, C.J.: *Excretion of Phenazopyridine and its Metabolites in the Urine of Humans, Rats, Mice, and Guinea Pigs.* J. Pharm. Sciences, **79**, No. 4 : (1990)

Thomas, R.J., Doddabele, S., and Kamad, A.B.: *Chronic Severe Hemolytic Anemia Related To Surreptitious Phenazopyridine Abuse.* Ann. Intern. Med., **121**: 308 (1994)

Tricker, P.: *Ancillary Use of Phenazopyridine (Pyridium) in Urinary Tract Infections.* Curr. Ther. Res., **12**, No. 7, 441-445 (1970)

Vriesekens, L. A. M., Stobberingh, E. E., Winkens, R. A. G., and Houben, A. W.: *Different Lengths of Treatment with Co-trimoxazole for Acute Uncomplicated Urinary Tract Infections in Women.* Brit. Med. J., **299**: 1319-1322 (1989)

Walther H.W.E.: *Urinary Antisepsis: Historical Review and Present Evaluation.* J.A.M.A., **109**: 999-1005 (1937)

Walther H.W.E.: *Clinical Application of Urinary Antisepsis.* South. M. J., **22**: 161 (1929)

Walther, H.W.E. and Willoughby, R.M.: *Oral Dye Therapy in Urogenital Infections.* Amer. J. Surg., **25**: 460-466 (1934)

Walton R.P. and Lawson, E.H. *Pharmacology and Toxicology of the Azo Dye, Phenylazo-alpha-alpha-diaminopyridine (Pyridium).* J. Pharmacol. Exp. Ther., **51**: 200-216 (1934)

Wander, H.J. and Pascoe, D.J. *Phenazopyridine Hydrochloride Poisoning. Report of Case and Review of Literature.* Am. J. Dis. Child., **110**: 105-107 (1965)

Ward, L.R., Rowe, B., and Threlfall, E.J. *Incidence of Trimethoprim Resistance in Salmonellae Isolated in Britain: A Twelve Year Study.* Lancet, **2**: 705-706 (1982).

Witzgall, H.: *Sulfonamidbindung an Bakterien.* 3rd Int. Congr. Chemother., Stuttgart, **1**: 609-611 (1963) (Thieme, Stuttgart 1964); see also:Struller, T.H.: *Progress in Sulfonamide Research*; in E. Jucker: Progress in Drug Research Vol. 12, 389-457 (Birkhäuser, Basel/Stuttgart 1968)

Wong, B. and Norman, D.C. *Evaluation of a Novel Medication Aid, the Calendar Blister-Pak, and its Effect on Drug Compliance in a Geriatric Outpatient Clinic.* J. American Geriatrics Soc., **35** No. 1: (January 1987)

Wren, B.G.: *Double-Blind Trial Comparing Trimethoprim-Sulfamethoxazole (Bactrim) with Ampicillin in Treating Urinary Infections.* Med. J. Aust. **1**: 261-263 (1972)

Yamamoto, K., Hirose, K., Eigyo, M., Jyoyaa, H., and Naito, Y.: *Studies on Sulfamethoxazole and Trimethoprim. Pharmacological Studies on Sulfamethoxazole, Trimethoprm, and their Mixture.* Chemotherapy, **21**: 187-196 (1973)

# Appendix Three

## Table VI-36

### Statistically Significant Hematology and Urinalysis Parameters Comparisons between Single-Treatment (Trimethoprim-Sulfamethoxazole DS or Phenazopyridine Hydrochloride) and Combination Treatment ( Trimethoprim-Sulfamethoxazole DS and Phenazopyridine Hydrochloride)

| Parameter | Day 6 PZP *and* TMP-SMZ Mean | Day 3 PZP Mean | PZP vs PZP *and* TMP-SMZ | | | Day 3 TMP-SMZ Mean | TMP-SMZ vs PZP *and* TMP-SMZ | | | Normal Values ** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Change* | % change | p-value | | Change* | % change | p-value | |
| **HEMATOLOGY** | | | | | | | | | | |
| Hemoglobin | 12.66 | 13.02 | -0.35 | -2.8 | 0.013 | 13.12 | -0.45 | -3.6 | 0.003 | 11.0-15.0 (gm/dL) |
| WBC | 7.16 | 8.13 | -0.96 | -13.4 | <0.001 | 7.68 | -0.52 | -7.2 | 0.045 | 4.0-10.0 ($x10^3$/uL) |
| Mean Corpuscular Hemoglobin | 29.44 | 29.78 | -0.35 | -1.2 | 0.003 | 29.89 | -0.45 | -1.5 | <0.001 | 28-34 (pg) |
| Mean Corpuscular Hemoglobin Concentration | 32.19 | 32.75 | -0.56 | -1.7 | <0.001 | 32.99 | -0.81 | -2.5 | <0.001 | 32.0-36.0 (%) |
| Mean Corp. Vol. | 91.64 | 91.08 | 0.56 | 0.6 | 0.055 | 90.72 | 0.93 | 1.0 | 0.003 | 83-99 (fl) |
| Segments | 57.09 | 62.54 | -5.46 | -9.6 | 0.006 | 59.46 | -2.37 | -4.2 | 0.221 | 49.0-80.0 (%) |
| Lymphocytes | 33.91 | 29.78 | 4.12 | 12.2 | 0.031 | 32.14 | 1.77 | 5.2 | 0.353 | 12.0-40.0 (%) |
| **URINALYSIS** | | | | | | | | | | |
| pH | 5.46 | 5.25 | 0.21 | 3.8 | 0.238 | 5.47 | -0.02 | -0.3 | 0.927 | 5.0-8.0 |

* Compared to combination therapy; **

Table VI-37

**Statistically Significant Clinical Chemistry Parameters Comparisons between Single-Treatment (Trimethoprim-Sulfamethoxazole DS or Phenazopyridine Hydrochloride) and Combination Treatment ( Trimethoprim-Sulfamethoxazole DS and Phenazopyridine Hydrochloride)**

| Parameter | Day 6 PZP *and* TMP-SMZ Mean | Day 3 PZP Mean | PZP vs PZP *and* TMP-SMZ | | | Day 3 TMP-SMZ Mean | TMP-SMZ vs PZP *and* TMP-SMZ | | | Normal Values ** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Change* | % change | p-value | | Change* | % change | p-value | |
| Triglycerides | 194.94 | 281.25 | -86.31 | -44.3 | 0.009 | 283.68 | -88.74 | -45.5 | 0.009 | 35-160 (mg/dL) |
| Chloride | 102.95 | 104.33 | -1.38 | -1.3 | 0.036 | 103.10 | -0.15 | -0.1 | 0.821 | 95-105 (mmol/L) |
| Anion Gap | 15.44 | 14.00 | 1.44 | 9.3 | 0.014 | 16.93 | -1.49 | -9.7 | 0.013 | 10-20 (mmol/L) |
| Creatinine | 1.13 | 0.91 | 0.22 | 19.8 | <0.001 | 1.04 | 0.09 | 8.1 | 0.002 | 0.5-1.4 (mg/dL) |
| BUN/Creatinine Ratio | 11.94 | 15.42 | -3.48 | -29.1 | <0.001 | 13.78 | -1.84 | -15.4 | 0.021 | 9.0-25.0 |
| Calcium | 9.45 | 9.55 | -0.10 | -1.1 | 0.194 | 9.66 | -0.21 | -2.3 | 0.013 | 8.5-10.5 (mg/dL) |
| Uric Acid | 2.99 | 3.62 | -0.62 | -20.9 | <0.001 | 3.36 | -0.37 | -12.4 | 0.005 | 1.2-7.5 (mg/dL) |
| Total Bilirubin | 0.63 | 0.57 | 0.05 | 8.3 | 0.047 | 0.48 | 0.14 | 22.7 | <0.001 | 0.2-1.2 (mg/dL) |
| Direct Bilirubin | 0.27 | 0.14 | 0.13 | 47.5 | 0.017 | 0.28 | -0.01 | -4.9 | 0.801 | 0.0-0.3 (mg/dL) |
| ndirect Bilirubin | 0.81 | 0.74 | 0.07 | 8.6 | 0.422 | 0.24 | 0.57 | 70.6 | <0.001 | 0.0-1.1 (mg/dL) |

Compared to combination therapy; *

**Table VI-40**

**Comparison of Day 2 to Day 5 Vital Signs**

**Mean Values and Analysis of Variance Results**

| ALL SUBJECTS | | | | |
|---|---|---|---|---|
| | Period 1 | | Period 2 | |
| | Regimen A (N=6) | | Regimen B (N=5) | |
| | Day 2 | Day 5 | Day 2 | Day 5 |
| Sequence A/B* | PZP | PZP/ TMP-SMZ | TMP-SMZ | TMP-SMZ/ PZP |
| Systolic B.P. (mm Hg) | 120.33 | 127.33 | 122.80 | 124.40 |
| Diastolic B.P. (mm Hg) | 75.00 | 83.00 | 72.80 | 71.60 |
| Heart Rate (beats/min) | 72.33 | 84.00 | 70.40 | 75.60 |
| Respiratory Rate (breaths/min) | 19.00 | 16.00 | 16.80 | 16.80 |
| Temperature (°F) | 97.02 | 98.92 | 96.98 | 96.50 |
| | Regimen B (N=6) | | Regimen A (N=6) | |
| | Day 2 | Day 5 | Day 2 | Day 5 |
| Sequence B/A** | TMP-SMZ | TMP-SMZ/ PZP | PZP | PZP/ TMP-SMZ |
| Systolic B.P. (mm Hg) | 119.00 | 117.00 | 117.67 | 111.00 |
| Diastolic B.P. (mm Hg) | 69.67 | 72.00 | 71.33 | 68.33 |
| Heart Rate (beats/min) | 72.33 | 74.00 | 69.33 | 69.33 |
| Respiratory Rate (breaths/min) | 19.00 | 16.00 | 16.00 | 16.33 |
| Temperature (°F) | 96.87 | 98.22 | 96.85 | 96.42 |

* Subjects receiving Regimen A in Period 1 and Regimen B in Period 2

** Subjects receiving Regimen B in Period 1 and Regimen A in Period 2

PZP: Phenazopyridine hydrochloride

TMP-SMZ: Trimethoprim-sulfamethoxazole DS

**Table VI-40 (continued)**

**Comparison of Day 2 to Day 5 Vital Signs**

**Mean Values and Analysis of Variance Results**

| Sequences and Period Pooled | | | | | |
|---|---|---|---|---|---|
| | **Regimen A** | **Regimen B** | **Regimen A** | **Regimen B** | **Regimen A and B** |
| | **Day 2** | **Day 2** | **Day 5** | **Day 5** | **Day 5** |
| | **PZP** | **TMP-SMZ** | **PZP/ TMP-SMZ** | **TMP-SMZ/ PZP** | **TMP-SMZ/ PZP** |
| | (N=12) | (N=11) | (N=12) | (N=11) | (N=23) |
| Systolic B.P. (mm Hg) | 119.00 | 120.73 | 119.17 | 120.36 | 119.74 |
| Diastolic B.P. (mm Hg) | 73.17 | 71.09 | 75.67 | 71.82 | 73.83 |
| Heart Rate (beats/min) | 70.83 | 71.45 | 76.67 | 74.73 | 75.74 |
| Respiratory Rate (breaths/min) | 17.50 | 18.00 | 16.17 | 16.36 | 16.26 |
| Temperature (°F) | 96.93 | 96.92 | 97.67 | 97.44 | 97.56 |

| Analysis of Variance Results | | | |
|---|---|---|---|
| | **Regimen A Day 5 vs. Regimen B Day 5** | **PZP Day 2 vs. Regimen A and Regimen B Day 5** | **TMP-SMZ Day 2 vs. Regimen A and Regimen B Day 5** |
| | p-value | p-value | p-value |
| Systolic B.P. (mm Hg) | 0.986 | 0.950 | 0.905 |
| Diastolic B.P. (mm Hg) | 0.094 | 0.887 | 0.195 |
| Heart Rate (beats/min) | 0.536 | 0.046 | 0.100 |
| Respiratory Rate (breaths/min) | 0.836 | 0.010 | 0.001 |
| Temperature (°F) | 0.492 | 0.053 | 0.048 |

PZP: Phenazopyridine hydrochloride; TMP-SMZ: Trimethoprim-sulfamethoxazole DS

## Table VI-41

## Comparison of Day 3 to Day 6 Vital Signs

## Mean Values and Analysis of Variance Results

| ALL SUBJECTS | | | | |
|---|---|---|---|---|
| | Period 1 | | Period 2 | |
| | Regimen A (N=6) | | Regimen B (N=5) | |
| | Day 3 | Day 6 | Day 3 | Day 6 |
| Sequence A/B* | PZP | PZP/ TMP-SMZ | TMP-SMZ | TMP-SMZ/ PZP |
| Systolic B.P. (mm Hg) | 125.33 | 121.00 | 124.40 | 122.40 |
| Diastolic B.P. (mm Hg) | 75.67 | 77.33 | 78.00 | 77.60 |
| Heart Rate (beats/min) | 74.67 | 78.67 | 74.00 | 73.20 |
| Respiratory Rate (breaths/min) | 18.67 | 16.67 | 16.40 | 17.20 |
| Temperature (°F) | 96.42 | 96.70 | 97.76 | 97.40 |
| | Regimen B (N=6) | | Regimen A (N=6) | |
| | Day 3 | Day 6 | Day 3 | Day 6 |
| Sequence B/A** | TMP-SMZ | TMP-SMZ/ PZP | PZP | PZP/ TMP-SMZ |
| Systolic B.P. (mm Hg) | 115.33 | 114.33 | 112.00 | 110.67 |
| Diastolic B.P. (mm Hg) | 67.33 | 68.33 | 70.67 | 71.67 |
| Heart Rate (beats/min) | 73.00 | 74.67 | 68.67 | 70.00 |
| Respiratory Rate (breaths/min) | 18.67 | 16.67 | 16.33 | 16.67 |
| Temperature (°F) | 96.57 | 96.83 | 96.68 | 95.90 |

* Subjects receiving Regimen A in Period 1 and Regimen B in Period 2
** Subjects receiving Regimen B in Period 1 and Regimen A in Period 2
PZP: Phenazopyridine hydrochloride
TMP-SMZ: Trimethoprim-sulfamethoxazole DS

**Table VI-41 (continued)**

**Comparison of Day 3 to Day 6 Vital Signs**

**Mean Values and Analysis of Variance Results**

| Sequences and Period Pooled | | | | | |
|---|---|---|---|---|---|
| | **Regimen A** | **Regimen B** | **Regimen A** | **Regimen B** | **Regimen A and B** |
| | **Day 3** | **Day 3** | **Day 6** | **Day 6** | **Day 6** |
| | **PZP** | **TMP-SMZ** | **PZP/ TMP-SMZ** | **TMP-SMZ/ PZP** | **TMP-SMZ/ PZP** |
| | **(N=12)** | **(N=11)** | **(N=12)** | **(N=11)** | **(N=23)** |
| Systolic B.P. (mm Hg) | 118.67 | 119.46 | 115.83 | 118.00 | 116.87 |
| Diastolic B.P. (mm Hg) | 73.17 | 72.18 | 74.50 | 72.55 | 73.57 |
| Heart Rate (beats/min) | 71.67 | 73.45 | 74.33 | 74.00 | 74.17 |
| Respiratory Rate (breaths/min) | 17.50 | 17.64 | 16.67 | 16.91 | 16.78 |
| Temperature (°F) | 96.55 | 97.11 | 96.30 | 97.09 | 96.68 |

| Analysis of Variance Results | | | |
|---|---|---|---|
| | **Regimen A Day 6 vs. Regimen B Day 6** | **PZP Day 3 vs. Regimen A and Regimen B Day 6** | **TMP-SMZ Day 3 vs. Regimen A and Regimen B Day 6** |
| | p-value | p-value | p-value |
| Systolic B.P. (mm Hg) | 0.584 | 0.428 | 0.385 |
| Diastolic B.P. (mm Hg) | 0.422 | 0.909 | 0.537 |
| Heart Rate (beats/min) | 0.865 | 0.233 | 0.721 |
| Respiratory Rate (breaths/min) | 0.840 | 0.189 | 0.184 |
| Temperature (°F) | 0.030 | 0.563 | 0.184 |

PZP: Phenazopyridine hydrochloride
TMP-SMZ: Trimethoprim-sulfamethoxazole DS

# TABLE II-75

## Adverse Events

| Subject # | Study Drug | Adverse Event | Severity | Relation-ship to Study Drug (s) | Onset | | Resolved | | Manage-ment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Date | Time | Date | Time | |
| 4 | TMP-SMZ First | Headache | Moderate | Possible | 10/11/97 | 1400 | 10/12/97 | 630 | Continued study |
| 8 | TMP-SMZ First | Constipation | Mild | Possible | 10/14/97 | 730 | 10/16/97 | 800 | Continued study |
| | | Vomit | Moderate | Possible | 10/15/97 | 1530 | 10/15/97 | 1530 | Continued study |
| 9 | TMP-SMZ First | Constipation | Mild | Possible | 10/14/97 | 830 | 10/16/97 | 800 | Continued study |
| | | Headache | Mild | Possible | 10/14/97 | 830 | 10/16/97 | 800 | Continued study |
| 10 | PZP First | Nausea | Mild | Unknown* | 10/15/97 | 1300 | 10/15/97 | 1500 | Continued study** |
| | | Vomit | Moderate | Unknown* | 10/15/97 | 1745 | 10/15/97 | 1745 | Continued study** |
| | | Headache | Moderate | Unknown* | 10/15/97 | 1845 | 10/16/97 | 800 | Continued study** |
| | | Pallor | Mild | Unknown* | 10/15/97 | 1845 | 10/16/97 | 800 | Continued study** |
| | | Nervousness | Mild | Unknown* | 10/15/97 | 1845 | 10/16/97 | 800 | Continued study** |
| 11 | TMP-SMZ First | Pain eye | Mild | Not related | 10/13/97 | 1100 | 10/15/97 | 800 | Continued study |
| | | Nausea | Mild | Possible | 10/13/97 | 1100 | 10/15/97 | 800 | Continued study |
| 12 | PZP First | Pharyngitis | Mild | Not related | 10/13/97 | 834 | 10/15/97 | 830 | Continued study |

TMP-SMZ: Trimethoprim-Sulfamethoxazole DS;
PZP: Phenazopyridine hydrochloride 200 mg
* The subject was found to be pregnant at check-in of Period 2; these adverse events are consistent with pregnancy.
** The subject continued and completed Period 1 of the study and was dismissed at check-in of Period 2 when results of her pregnancy test, performed at entry of Period 2 were positive

## TABLE II-76

### Summary of Adverse Events by Body System

| | PZP* | PZP + TMP/SMZ† | TMP/SMZ** | TMP/SMZ + PZP‡ |
|---|---|---|---|---|
| Number of Subjects | 12 | 12 | 11 | 11 |
| Number of Subjects Reporting Events | 1 (8%) | 1 (8%) | 2 (18%) | 2 (18%) |
| Number of Events Reported | 1 | 5 | 3 | 4 |
| Number of Subjects Reporting | | | | |
| 0 Events | 11 ( 92%) | 11 ( 92%) | 9 ( 82%) | 9 ( 82%) |
| 1 Event | 1 ( 8%) | 0 ( 0%) | 1 ( 9%) | 0 ( 0%) |
| >1 Event | 0 ( 0%) | 1 ( 8%) | 1 ( 9%) | 2 ( 18%) |
| **Total** | 12 (100%) | 12 (100%) | 11 (100%) | 11 (100%) |
| Severity of Event | | | | |
| Mild | 1 (100%) | 3 ( 60%) | 2 ( 67%) | 3 ( 75%) |
| Moderate | 0 ( 0%) | 2 ( 40%) | 1 ( 33%) | 1 ( 25%) |
| **Total** | 1 (100%) | 5 (100%) | 3 (100%) | 4 (100%) |
| Relationship of Event to Study Drug | | | | |
| Unknown | 0 ( 0%) | 5 (100%) | 0 ( 0%) | 0 ( 0%) |
| Possibly | 0 ( 0%) | 0 ( 0%) | 2 ( 67%) | 4 (100%) |
| Not Related | 1 (100%) | 0 ( 0%) | 1 ( 33%) | 0 ( 0%) |
| **Total** | 1 (100%) | 5 (100%) | 3 (100%) | 4 (100%) |
| Body System*** | | | | |
| *Digestive System* | 0 ( 0%) | 1 ( 8%) | 1 ( 9%) | 2 ( 18%) |
| Constipation | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) | 2 ( 18%) |
| Nausea | 0 ( 0%) | 1 ( 8%) | 1 ( 9%) | 0 ( 0%) |
| Vomit | 0 ( 0%) | 1 ( 8%) | 0 ( 0%) | 1 ( 9%) |
| *Body as a Whole* | 0 ( 0%) | 1 ( 8%) | 1 ( 9%) | 1 ( 9%) |
| Headache | 0 ( 0%) | 1 ( 8%) | 1 ( 9%) | 1 ( 9%) |
| *Cardiovascular System* | 0 ( 0%) | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) |
| Pallor | 0 ( 0%) | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) |
| *Nervous System* | 0 ( 0%) | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) |
| Nervousness | 0 ( 0%) | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) |
| *Respiratory System* | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) |
| Pharyngitis | 1 ( 8%) | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) |
| *Special Senses* | 0 ( 0%) | 0 ( 0%) | 1 ( 9%) | 0 ( 0%) |
| Pain eye | 0 ( 0%) | 0 ( 0%) | 1 ( 9%) | 0 ( 0%) |

PZP: Phenazopyridine Hydrochloride(200 mg); TMP/SMZ: Trimethoprim/Sulfamethoxazole DS (160 mg/800 mg)

* PZP administered alone for Days 1 - 3

** TMP/SMZ administered alone for Days 1 - 3

*** Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition Body System. At each level of summarization (body system or event), subjects are only counted once

† Combination of PZP + TMP/SMZ administered Days 4 - 6 with PZP administered alone for Days 1 - 3

‡ Combination of TMP/SMZ + PZP administered Days 4 - 6 with TMP/SMZ administered alone for Days 1 - 3

# Appendix Four

## TABLE VIII-106

## COMPILED CUMULATIVE SAFETY DATA FOR TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| | Dose regimen with trimethoprim-sulfamethoxazole | | | |
|---|---|---|---|---|
| | Single-dose | 3-day | 5-day or 7-day[a] | 10-day |
| **ADVERSE EFFECTS** (No. of patients with adverse effects/total number; percent in parenthesis) | | | | |
| Gastrointestinal effect | 26/390 (6.7) | 28/297 (9.4) | 92[b]/1,020 (9.0) | 30/511 (5.9) |
| Allergic reaction | 8/390 (2.0) | 7/297 (2.3) | 38[c]/1,020 (3.7) | 48[d]/511 (9.4) |
| Vaginitis | 9/390 (2.3) | 2/297 (0.7) | 15/1,020 (1.5) | 30/511 (5.9) |
| Neurological | 3/390 (0.77) | 9/297 (3.0) | 14/1,020 (1.4) | 10/511 (2.0) |
| Other | 1/390 (0.26) | 8/297 (2.7) | 20/1,020 (2.0) | 3/511 (0.6) |
| Teratogenic effect | | | 4/120 [e] | |
| **PATIENT CHARACTERISTICS** (Breakdown of total number of patients by gender/age) | | | | |
| Male/Female | 365, F;<br>25, gender not reported | 297, All female | 625, F;<br>395, gender not reported | 393, F;<br>118, gender not reported |
| Mean age (years)[f] | 31 | 36 | 42[g] | 32 |

Gastrointestinal effects include nausea, vomiting, diarrhea, dyspepsia, constipation; allergic reactions include rash, swelling, sores; neurological reactions include malaise, headache, dizziness, lightheadedness, vertigo. "Other" is not defined by the investigators.

Counts *et al* (1982) reported 15 patients with adverse effects out of 48 in the group receiving 10-day therapy with TMP-SMZ, of which 7 were serious, requiring discontinuation of therapy or specific treatment; further, 6 patients out of 47 in the single-dose treatment group reported adverse events, of whom 4 were serious adverse events. They do not specify the kinds of adverse events. The data from this study are not included in the above Table.

[a] 4 patients died, all in the same study [redacted] all unrelated to administration of trimethoprim-sulfamethoxazole; 2 died of carcinomatosis, 1 of a cerebrovascular accident, and 1 of chronic renal failure

[b] 4 discontinued therapy due to GI upset, 1 had a severe condition.

[c] 4 discontinued therapy due to rash, 1 had a severe condition

[d] Of 23 patients, all in the same study [redacted] most had morbilliform erythema or urticaria, necessitating cessation of therapy

[e] [redacted] of 186 pregnant women studied for teratogenic effects, there was no evidence of increase in fetal abnormalities in the patients who received active treatment (n = 120) compared to those who received placebo (n = 66) (3.3% in treatment versus 4.5% in placebo)

[f] The ages of patients ranged from 12-78 years, and varied for each study (some had a college-age population, others had an older population, others had a population with an age range spanning 16-78 years)

[g] The ages of 188 patients in this group were not reported

## TABLE VIII-108

## COMPILED CUMULATIVE SAFETY DATA FOR PHENAZOPYRIDINE HYDROCHLORIDE

| Adverse effect | # patients | Male/Female | Age (years) | Duration of treatment | Comments |
|---|---|---|---|---|---|
| No adverse effects | 167 | 17 M, 32 F, 118, NR | 49 patients with a mean of 25 years; remaining 118, NR | 3 days to 2 weeks | Drug administered per manufacturer's instructions |
| Does not cause cancer | 2,214 | NR | NR | NR | Retrospective analysis and follow-up of patients who had been administered Pyridium |
| Anorexia and nausea | "Occasional" out of 1,500 | NR | NR | 7 day regimen given intermittently for 1 to 2.5 mos. | Number of patients with adverse events not specified |
| Drowsiness, dry mouth, dizziness | 20 out of 99 | 73 M, 26 F | "Older age group" | 2 days | Drug was Dolonil®, in which phenazopyridine hydrochloride is one component out of 3 |
| Renal failure | 3 | 1 M, 2 F | 75 and above | Up to 12 days | Previous impairment of renal function |
| Urinary stones | 2 | 2 M | > 55 | 5 mo. to 2 yrs. | Long-term use of Pyridium |
| Hepatitis hypersensitivity | 4 | 4 F | 3 young adults, one 66 yr. old | 2 had taken Pyridium on > 4 occasions spanning a few years; 2 for 3-10 days | Condition improved, liver enzymes normal upon drug withdrawal |
| Methemoglobinemia | 7 | 4 M, 3 F | 3-73 | 5 had long-term use (24 days or more); 2 were administered drug for 9-11 days | 5 had long-term use (including one chronic user), the 3-yr. old was given high doses for 11 days, and 1 adult had previous renal failure; condition of all improved with treatment |

NR = Not reported

## TABLE VIII-108 (Continued)

## COMPILED CUMULATIVE SAFETY DATA FOR PHENAZOPYRIDINE HYDROCHLORIDE

| Adverse effect | # patients | Male/Female | Age (years) | Duration of treatment | Comments |
|---|---|---|---|---|---|
| Methemoglobinemia due to overdose | 4 | 4 F | 13 mos. to 3 yrs. | Accidental overdose | Methemoglobinemia reversed upon gastric lavage and administration of methylene blue |
| No adverse effects | 167 | 17 M, 32 F, 118, NR | 49 patients with a mean of 25 years; remaining 118, NR | 3 days to 2 weeks | Drug administered per manufacturer's instructions |
| Does not cause cancer | 2,214 | NR | NR | NR | Retrospective analysis and follow-up of patients who had been administered Pyridium |

NR = Not reported

# Appendix Five

## TABLE VIII-31

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH A CONCURRENT PLACEBO CONTROL** | | | | | | | | |
| Fihn, S. D., Johnson, C., Roberts, P. L., Running, K., and Stamm, W. E. Ann. Intern. Med., 108: 350-357 (1988) | Vol. 1.16 Pages: 4625-4631 | U.S. (Seattle, WA) | Double-blind, randomized, placebo-controlled study | TMP-SMZ (double strength) 160 mg : 800 mg, 2 tablets followed by placebo b.i.d (single-dose); 2 placebos followed by TMP-SMZ b.i.d. (10-day) | TMP-SMZ, (single-dose), 126; TMP-SMZ, 10-day, 129 | Single-dose, 24.5 ± 3.5; 10-day, 24.5 ± 4.2 | All female | 10 days |
| Trienekens, T. A. M., Stobberingh, E. E., Winkens, R. A. G., and Houben, A. W. Brit. Med. J., 299: 1319-1322 (1989) | Vol. 1.16 Pages: 4632-4635 | Foreign (The Nether-lands) | Double-blind, randomized, placebo-controlled study | Cotrimoxazole, 960 mg for 3 days followed by 4 days of placebo, b.i.d (3-day regimen); Cotrimoxazole 960 mg b.i.d. for 7 days (7-day regimen) | 3-day group, 161; 7-day group, 166 | Mean ages: 3-day group, 35; 7-day group, 38.4 | All female | 7 days |
| **STUDIES WITH DOSE COMPARISON CONCURRENT CONTROL** | | | | | | | | |
| Counts, G. W., Stamm, W. E., McKevitt, M., Running, K., Holmes, K. K., and Turck, M. Rev. Inf. Dis., 4: 484-490 (1982) | Vol. 1.16 Pages: 4636-4638 | U.S. (Seattle, WA) | Randomized study | TMP-SMZ, 80 mg : 400 mg, 4 tablets in a single dose; or TMP-SMZ, 80 mg : 400 mg, 2 tablets every 12 hr. | Single-dose group, 38; 10-day group, 39 | Mean ages: Single-dose group, 41.6 (range, 18-74); 10-day group, 38.5 (range 19-72) | All female | Single dose or 10 days |

## TABLE VIII-31 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH DOSE COMPARISON CONCURRENT CONTROL (CONTINUED)** | | | | | | | | |
| Schultz, H. J., and McCaffrey, L. A. Mayo Clin. Proc., 59: 391-397 (1984) | Vol. 1.16 Pages: 4639-4643 | U.S. (Rochester, MN) | Randomized study | TMP-SMZ, 160 mg: 800 mg, 3 tablets in a single dose; or TMP-SMZ, 160 mg : 800 mg, b.i.d. | 68 patients with UTI in each group; 51 patients with urethral syndrome | Age range: 18-55 | All female | Single dose or 10 days |
| Greenberg, R. N., Reilly, P. M., Luppen, K. L., Weinandt, W. J., Ellington, L. L., and Bollinger, M. R. J. Infect. Dis., 153 (2): 277-282 (1986) | Vol. 1.16 Pages: 4644-4647 | U.S. (St. Louis, MO) | Randomized study | Group 1: cefadroxil, 1000 mg, single-dose; Group 2: cefadroxil, 500 mg b.i.d.; Group 3: cefadroxil, 500 mg, b.i.d.; Group 4: TMP-SMZ, 330: 1600 mg, single-dose; Group 5: TMP-SMZ, 160 : 800 mg, b.i.d. | Group 1, 20; Group 2, 26; Group 3, 28; Group 4, 26; Group 5, 26 | Mean ages Group 1, 28; Group 2, 32; Group 3, 33; Group 4, 34; Group 5, 32 | All female | Group 1, single-dose; Group 2, 3 days; Group 3, 7 days; Group 4, single-dose; Group 5, 3-days |
| Brumfitt, W. and Pursell, R. J. Infect. Dis., 128 (suppl): S657-S663 (1973) | Vol. 1.16 Pages: 4648-4652 | Foreign (London, Birmingham, UK) | Double-blind study | **Study 1**: TMP-SMZ in 3 doses b.i.d.: (250 mg: 500 mg; 160 mg: 800 mg; and 100 mg : 1000 mg) **Study 2**: Ampicillin, 1 g b.i.d.; Cephalexin, 1 g b.i.d.; TMP, 200 mg b.i.d.; TMP-SMZ, 160 mg : 800 mg, 2 tablets b.i.d. **Study 3**: Same as Study 2. | **Study 1**: 109 **Study 2**: Ampicillin, 33; Cephalexin, 31; TMP, 34; TMP-SMZ, 30 **Study 3**: 107 courses in 96 patients: Ampicillin, 27; Cephalexin, 26; TMP, 23 ; TMP-SMZ, 31 | NS | All female | 7 days |

## TABLE VIII-31 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH DOSE COMPARISON CONCURRENT CONTROL (CONTINUED)** | | | | | | | | |
| Brumfitt, W. and Pursell, R. Brit. Med. J., 2: 673-676 (1972) | Vol. 1.16 Pages: 4653-4658 | Foreign (London, UK) | Double-blind randomized study | Ampicillin, 1 g b.i.d.; Cephalexin, 1 g b.i.d.; TMP, 200 mg b.i.d.; TMP-SMZ, (160 mg: 800 mg), 2 tablets b.i.d. | 339 courses of treatment Ampicillin, 88; Cephalexin, 84; TMP, 83; TMP-SMZ, 84 | NS | 282 female 18 male | 7 days |
| Gruneberg, R. N. and Kolbe, R. Brit. Med. J. 1: 545-547 (1969) | Vol. 1.16 Pages: 4659-4662 | Foreign (London, UK) | Randomized trial | Grp.1: SMZ, 1 g b.i.d.; Grp. 2: TMP-SMZ, 100 mg : 1000 mg b.i.d.; Grp. 3: TMP-SMZ, 160 mg : 800 mg, b.i.d. | Grp. 1, 29; Grp. 2, 37; Grp. 3, 39 | Mean ages: Grp. 1, 62.1; Grp. 2, 67.4; Grp. 3, 65.8 | Grp. 1, 28% male; Grp. 2, 24% male; Grp. 3, 23% male | 5 days |
| Leibovici, L., Laor, A., Alpert, G., and Kalter-Leibovici, O. Israel J. Med. Sci., 20 257-259 (1984) | Vol. 1.16 Pages: 4663-4664 | Foreign (Israel) | Randomized study | TMP-SMZ, 480 : 2400 mg, single-dose; TMP-SMZ, 160 :800 mg, b.i.d. | TMP-SMZ, single-dose, 31; TMP-SMZ, 7-day, 32 | TMP-SMZ, single-dose, 20 ± 2.3 (range 18-29); TMP-SMZ, 7-day, 19.2 ± 1.0 (range 18-23) | All female | Single dose or 7 days |
| Masterton, R. G., and Bochsler, J. A. J. Antimicrob. Chemother. 35: 129-137 (1995) | Vol. 1.16 Pages: 4665-4670 | Foreign (U.K.) | Double-blind, randomized, multi-center study | Co-amoxiclav, 3.25 g, single-dose; Cotrimoxazole, 960 mg b.i.d. | Co-amoxiclav, single-dose, 144; Cotrimoxazole, 7-day, 135 | Mean ages: Co-amoxiclav, single-dose, 38; Cotrim-oxazole, 7-day, 38.9 | All female | Single dose or 7 days |

## TABLE VIII-31 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH DOSE COMPARISON CONCURRENT CONTROL (CONTINUED)** | | | | | | | | |
| Reeves, D. S., Faiers, M. C., Pursell, R. E., and Brumfitt, W. Brit. Med. J., 1: 541-544 (1969) | Vol. 1.16 Pages: 4671-4674 | Foreign (U.K.) | Randomized study | **Study 1**: Grp. 1: TMP-SMZ (125 : 250 mg) 2 tablets b.i.d.; Grp. 2: TMP-SMZ (50 : 500 mg) 2 tablets b.i.d. **Study 2**: Grp. 1: TMP-SMZ (80 : 400 mg) 2 tablets b.i.d.; Grp. 2: Ampicillin, 500 mg t.i.d.; Grp. 3: sulfadimidine, 1 g q.i.d. | **Study 1**: Grp. 1, 65; Grp. 2, 48 **Study 2**: Grp. 1, 41; Grp. 2, 30; Grp. 3, 35 | Mean ages: **Study 1**: Grp. 1, 66; Grp. 2, 61 **Study 2**: Grp. 1, 58; Grp. 2, 60; Grp. 3, 56 | Percent females: **Study 1**: Grp. 1, 72%; Grp. 2, 81% **Study 2**: Grp. 1, 71%; Grp. 2, 80%; Grp. 3, 77% | 7 days |
| Gossius, G., and Vorland, L. Scand. J. Infect. Dis., 16: 373-379 (1984) | Vol. 1.16 Pages: 4675-4678 | Foreign (Norway) | Randomized study | Grp. A: TMP-SMZ (320 : 1600 mg), single-dose of 4 tablets; Grp. B: TMP-SMZ (160 : 800 mg), 2 tablets, b.i.d.; Grp. C: TMP-SMZ (160 : 800), 2 tablets, b.i.d. | Grp. A: 93; Grp. B: 91; Grp. C: 95 | Mean age: Grp. A: 37.4; Grp. B: 36.9; Grp. C: 38.2 | All female | Grp. A: single-dose; Grp. B: 3 days; Grp. C: 10 days |
| Jones, R. H. J. Royal Coll. Gen. Pract. 33: 585-589 (1983) | Vol. 1.16 Pages: 4679-4681 | Foreign (U.K.) | Randomized study | Grp. A: TMP, 100 mg, 2 tablets, b.i.d. for 7 days; Grp. B: TMP, 100 mg, 4 tablets, single-dose; Grp. C: cotrimoxazole (80 mg TMP, 400 mg SMZ), 2 tablets b.i.d. for 7 days; Grp. D: cotrimoxazole, 4 tablets, single-dose | Grp. A: 27; Grp. B, 25; Grp. C, 28; Grp. D, 25 | Mean age, 41.8 (range 14-71) | 97 female, 8 male | Single-dose or 7 days |

## TABLE VIII-31 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES USING AN ACTIVE CONCURRENT CONTROL** | | | | | | | | |
| Gleckman, R. A. J. A. M. A.., 233: 427-431 (1975) | Vol. 1.16 Pages: 4682-4685 | U.S. (Multi-center) | Double-blind, randomized study | TMP-SMZ, 320 : 1600 mg; Ampicillin, 2 g in divided doses each day | TMP-SMZ, 77; Ampicillin, 86 | Median ages: TMP-SMZ, 45; Ampicillin, 51 | TMP-SMZ, 27.3% male. Ampicillin. 29.1% male | 10 days |
| Iravani, A., Richard, G. A., Baer, H., and Fennel, R. Antimicrob. Agents Chemother., 19 (4): 598-604 (1981b) | Vol. 1.16 Pages: 4686-4688 | U.S. (Gaines-ville, FL) | Randomized trial | Nalidixic acid (NA), 1 g q.i.d.; TMP-SMZ, 160 mg : 800 mg, b.i.d. | NA, 71; TMP-SMZ, 64 | Mean age: 23 ± 4 | All female | NA, 7 days; TMP-SMZ, 10 days |
| Hooton, T. M. et. al. Antimicrob. Agents Chemother. 35(7): 1479-1483 (1991) | Vol. 1.16 Pages: 4689-4693 | U.S. (Seattle, WA) | Randomized study | Ofloxacin (400 mg) single-dose; or ofloxacin (200 mg) once daily; or TMP-SMZ (160 mg: 800 mg), b.i.d. | Ofloxacin, single-dose, 48; ofloxacin, 3-day, 49; TMP-SMZ, 47 | Mean age: Ofloxacin, single-dose, 25; ofloxacin, 3-day, 25; TMP-SMZ, 24 | All female | Ofloxacin as single-dose or 3-day regimen; TMP-SMZ for 7 days |
| Fair, W. R., Crane, D. B., Peterson, L. J., Dahmer, C., Tague, B., and Amos, W. J. Urol., 123: 717-721 (1980) | Vol. 1.16 Pages: 4694-4696 | U.S. (St. Louis, MO) | Randomized study | Penicillin - G, 800,000 units, q.i.d.; TMP-SMZ, b.i.d. | Penicillin - G, 3-day, 15; Penicillin - G, 10-day, 15; TMP-SMZ, 3-day, 15; TMP-SMZ, 10-day, 15 | 18-69 | All female | 3 days or 10 days |

## TABLE VIII-31 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| STUDIES USING AN ACTIVE CONCURRENT CONTROL (CONTINUED) | | | | | | | | |
| Wren, B. G. Med. J. Aust. 1: 261-263 (1972) | Vol. 1.16 Pages: 4697-4698 | Foreign (New South Wales, Australia) | Double-blind randomized study | Ampicillin, 250 mg, 2 capsules q.i.d.; TMP-SMZ, 320 mg : 1600 mg per day in divided doses | Ampicillin, 42; TMP-SMZ, 41 | NS | All female | 5-8 days |
| Cartwright, K. A., Stanbridge, T. N., and Cooper, J. The Practitioner, 226: 152-156 (1982) | Vol. 1.16 Pages: 4699-4702 | Foreign (U. K.) | Randomized, blinded | TMP, 300 mg, once daily; Cotrimoxazole, 2 tablets b.i.d. | TMP, 60; Cotrimoxazole, 49 | Mean ages: TMP, 38 (range 16-67); Cotrimoxazole, 40 (range 16-78) | TMP, all female; Cotrim-oxazole, 5 male, 44 female | 7 days |

UTI = Urinary tract infection

APPEARS THIS WAY
ON ORIGINAL

## TABLE VIII-32

## SUMMARY OF REVIEW ARTICLES ON TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Number of studies reviewed | Drugs/doses studied | Comments/conclusions |
|---|---|---|---|---|
| Johnson, J. R. and Stamm, W. E. Ann. Intern. Med., 111: 906-917 (1989) | Vol. 1.16 Pages: 4703-4705 | NR | Several antibiotics including cephalosporins, β-lactam antibiotics, aminoglycosides, quinolones, and folate antagonists, i.e., TMP-SMZ; evaluated as single-dose and multi-day therapy | The data from several publications on the use of TMP-SMZ for the treatment of cystitis suggest that single-dose therapy with TMP or TMP-SMZ effectively eradicates most occult renal infections, but that 10-day therapy might be even more effective. Furthermore, the relapses were much lower with long-term treatment compared to single-dose therapy. Higher cure rates were observed with TMP and TMP-SMZ, compared with ampicillin and other agents, regardless of the site of infection or the duration of therapy. |
| Leibovici, L., and Wysenbeek, A. J. Qtrly J. Med.,News Series 78, No. 285: 43-57 (1991) | Vol. 1.16 Pages: 4706-4707 | 25 | Comparison of single-dose versus conventional therapy (5 days or longer) in the treatment of UTI | Single-dose treatment of urinary tract infection in women is less effective than conventional treatment, but causes fewer side effects. While all but 4 out of 34 studies since 1967 have concluded that single-dose treatment is as effective as conventional therapy in the treatment of symptomatic uncomplicated UTI in women, none of them had a large enough sample to achieve an 80% certainty of detecting a difference of 15% in cure rates at a 5% level of significance. Conventional therapy will probably save costs associated with repeated clinic visits and laboratory tests. |
| Norrby, S. R. Rev. Infect. Dis., 12: 458-467 (1990) | Vol. 1.16 Pages: 4708-4709 | 28 | Single-dose versus 3-day or 5-day treatment of UTI with various antibiotics | With all antibiotics, a single-dose was less efficient than a 3-day or a ≥ 5-day treatment in eradicating bacteriuria. With TMP-SMZ, there appeared to be no benefit of treating beyond 5 days. Also, adverse reactions increased markedly when treatment was given for >3 days. In conclusion, single-dose treatment is less efficient than treatment for ≥ 3 days, β-lactams should be administered for ≥ 5 days, the optimal duration for trimethoprim/sulfonamide appears to be 3 days, and considerable differences exist among various antibiotics. |

UTI = urinary tract infection

## TABLE VIII-32 (Continued)

## SUMMARY OF REVIEW ARTICLES ON TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

| Investigators, Publications | Full report Data listings | Number of studies reviewed | Drugs/doses studied | Comments/conclusions |
|---|---|---|---|---|
| Philbrick, J. T., and Bracikowski, J. P. Arch. Int. Med., 145: 1672-1678 (1985) | Vol. 1.16 Pages: 4710-4711 | 14 | Comparison of single-dose versus conventional multi-dose treatment for UTI | Twelve of fourteen randomized trials of single-dose antimicrobial therapy for uncomplicated UTI concluded that single-dose therapy was as effective as conventional multiple-dose therapy. Although the studies were carefully conducted none reported or ascertained in a blinded manner the incidence of adverse drug reactions. Also, no study included enough patients to prevent a Type II error. Single-dose therapy with amoxicillin (3 g) was significantly less effective than multidose therapy, while single-dose TMP-SMZ (2 or 3 double-strength tablets) was indistinguishable from multidose therapy although there were still too few patients to exclude Type II error. More research is needed with greater attention to sample size and blinded determination of adverse effects before a conclusion can be reached regarding the suitability of single-dose therapy. |

UTI = urinary tract infection

## TABLE VIII-90

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH A CONCURRENT PLACEBO CONTROL** | | | | | | | | |
| Trickett, P.C. Curr. Ther. Res., 12: No. 7, 441-445 (1970) | Vol. 1.16 Pages: 4723-4726 | U. S. (New Orleans, LA) | Randomized, Placebo-controlled | Drug, 100 mg Pyridium; Placebo (methylene blue), 10 mg Both given as 2 tablets t.i.d. before meals | Drug, 49; Placebo, 51 | Drug, 25; Placebo, 26 | Drug, 17/32; Placebo, 22/28 | 3 days |
| Braitberg, L. D. J. Lab. & Clin. Med., 26: 1768-1773 (1941) | Vol. 1.16 Pages: 4727-4729 | U. S. (Chicago, IL) | Patients with placebo were included | Pyridium, 600-900 mg daily | Drug, 40; Placebo, 5 | NR | 36/4 | Approx. 2 weeks |
| **STUDIES WITH A NO-TREATMENT CONCURRENT CONTROL** | | | | | | | | |
| Kirwin T. J, Lowsley O. S., Menning, J. Am. J. Surg., 62: 330-335 (1943) | Vol. 1.16 Pages: 4730-4731 | U. S. (New York, NY) | Patients were given the drug and its effect was monitored | Pyridium, 2 tablets (100 mg each) t.i.d. | Drug: 118 | NR | NR | 2 weeks or longer |
| Mason, L. M. Va. Med. Monthly, 58: 190-194 (1931) | Vol. 1.16 Page: 4732 | U. S. (Virginia) | Patients were given the drug and its effect was monitored | Pyridium, 1 or 2 tablets (100 mg each) after meals; or a 0.5-1.0% liquid instillation | Drug: 15 | NR | 12/3 | 1 week to a few months |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH A NO-TREATMENT CONCURRENT CONTROL (CONTINUED)** | | | | | | | | |
| Morrissey, J. H. and Spinelli, A. N. J. Urol., 44: 381-385 (1940) | Vol. 1.16 Pages: 4733-4736 | U. S. (New York, NY) | Patients were given the drug and its effect was monitored | For analgesic study: Pyridium, 100 mg tablets t.i.d.; For pre- and post-operative cases, drug given prior to, and after operation; For anesthetic study, 1 oz. of 1% solution, 2X | Analgesic study, 80; pre- and post-operative cases, 19; anesthetic study, 130 | Analgesic study: 17-82 (Mean, 34 years) | 72/8 | Analgesic study, duration of hospitalization: for operative cases, 2 single doses, one before and one after operation; for anesthetic study, 2 single doses before procedure |
| Reynolds, J. S., Wilkey, J. L., and Choy, J. K. L. Illinois Med . J., 78: 544-547 (1940) | Vol. 1.16 Pages: 4737-4739 | U. S. (Chicago, IL) | Patients were given the drug and its effect was monitored | Pyridium, 2 tablets (100 mg each) t.i.d. | 183 | NR | NR | 2 weeks |
| Spinelli, A. N., Keshin, J. G., and Davis, J. E. J. Amer. Geriat. Soc., 12: 771-775 (1964) | Vol. 1.16 Pages: 4740-4743 | U. S. (New York, NY) | Patients were given the drug and its effect was monitored | Drug: Dolonil (150 mg phenazopyridine, 0.3 mg *l*-hyoscyamine, and 15 mg butabarbital): 1 tablet after each meal and at bedtime | 99 | Older age group | 73/26 | 12-24 hours |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH A NO-TREATMENT CONCURRENT CONTROL (CONTINUED)** | | | | | | | | |
| Walther, H. W. E. and Willoughby, R. M. Amer. J. Surg., 25: 460-466 (1934) | Vol. 1.16 Pages: 4744-4745 | U. S. (New Orleans, LA) | Patients were given the drug and its effect was monitored | Pyridium, 200 mg t.i.d. | 1,500 | NR | NR | 7-day regimen (given intermittently for 1 to 2.5 months) |
| **STUDIES USING AN ACTIVE CONCURRENT CONTROL** | | | | | | | | |
| Walther H. W. E. South. M. J., 22: 161 (1929) | Vol. 1.16 Pages: 4746-4747 | U. S. (New Orleans, LA) | Patients were given Pyridium and its effect was monitored; mercuro-chrome, neutral acriflavine, and hexylresorcinol were also compared | Pyridium, 100 mg, 2 tablets t.i.d. after meals; Other medications, doses NR | Pyridium, 50 | 9-77 years (median age: 35 years) | Pyridium, 28/22 | 10 days or longer |
| **CASE REPORTS** | | | | | | | | |
| Crawford, S. E., Moon, A. E., Jr., Panos, T. C. and Hooks, C. A. J.Am. Med. Assoc., 146: 24-25 (1951) | Vol. 1.16 Page: 4748 | U.S. (Galveston, TX) | Case study of 1 patient | Pyridium, 100 mg q.i.d. followed by 100 mg every 3 hours (adult dose) | 1 | 3 | M, W | 100 mg q.i.d. for up to 7 days; 100 mg every 3 hours for 4 days |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS (Continued)** | | | | | | | | |
| Crawford, E. D. and Mulvaney, W. P. J. of Urol., 119: 280-281 (1978) | Vol. 1.16 Page: 4749 | U. S. (Los Angeles, CA) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 55 | M | ~ 5 months |
| Eybel, C. E., Armbruster, K. F. W., and Ing, T. S. J.A.M.A, 228: 1027-1928, (1974) | Vol. 1.16 Page: 4750 | U. S. (Chicago, IL) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 85 | F, W | 12 days |
| Fincher, M. E., and Campbell, H. T. Southern Med. J, 82: 372-374, (1989) | Vol. 1.16 Page: 4751 | U. S. (Augusta, GA) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 21 | M, W | 9 days |
| Friedman, G. D. and Ury, H. K. J. Natl. Cancer Inst., 65: 723-733 (1980) | Vol. 1.16 Page: 4752 | U. S. (Oakland, CA) | Review of 2,214 patients over a 4-year period | Pyridium, dose not specified | 2,214 | NR | "Ethnic-ally diverse" | NR (typical prescription s) |
| Goldfinger, S. E. and Marx, S. New Engl. J. Med., 286, No. 20: 1090-1091 (1972) | Vol. 1.16 Page: 4753 | U. S. (Boston, MA) | Case study of 2 patients | Pt. #1, dosed on 3 occasions;<br>Pt. #2, Pyridium, 600 mg per day | 1<br>1 | Pt. #1, 66;<br>Pt. #2, 30 | Pt. #1, F;<br>Pt. #2, F | Pt. # 1, 2-3 days;<br>Pt. #2, 10 days |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS (Continued)** | | | | | | | | |
| Greenberg, M. S. and Wong, H. New Eng. J. Med., 271: 431-435 (1964). | Vol. 1.16 Page: 4754 | U. S. (Boston, MA) | Case study of 2 patients | Pt. #1, Pyridium, 200 mg t.i.d.; Pt. #2, Pyridium, 200 mg t.i.d. | 1<br>1 | Pt. #1, 83; Pt. #2, 62 | Pt. #1, F; Pt. #2, F | Pt. #1, 37 days; Pt. #2, 24 days |
| Greenberg, M. S. Arch. Intern. Med., 136: 153-155 (1976) | Vol. 1.16 Page: 4755 | U. S. (Boston, MA) | Case study of 2 patients | Pt. #1, Pyridium, 900 mg daily; Pt. #2, Pyridium, 600 mg daily | 1<br>1 | Pt. #1, 52; Pt. #2, 62 | Pt. #1, F; Pt. #2, M | Pt. #1, 28 days; Pt. #2, 55 days |
| Mulvaney, W. P., Beck, C. W., and Brown, R. R. J. A. M. A., 221:1511-1512 (Sept 25, 1972). | Vol. 1.16 Page: 4756 | U. S. (Cincinnati, OH) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 67 | M | 2 years |
| Noonan, H. M., Kimbrell, M., Johnson, W. B., and Reuler, J. B. Urol., 21: 623-624 (1983) | Vol. 1.16 Page: 4757 | U. S. (Portland, OR) | Case study of 1 patient | Pyridium, 100 mg b.i.d. for 5 months, followed by 400 mg t.i.d. for 3 weeks | 1 | 89 | M | Over 5 months |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS (Continued)** | | | | | | | | |
| Ponte, C. D., Lewis, M. J., and Rogers II, J. S. Ann. of Pharmacother., 23:140-142 (1989) | Vol. 1.16 Page: 4758 | U. S. (Morgantown, WV) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 27 | F, W | Multiple courses over ~4 months |
| Terrell, J. R., Spruill, W. J., and Parish, R. C. Drug Intell. Clin. Pharm., 22: 915 (1988) | Vol. 1.16 Page: 4759 | U. S. (Athens, GA) | Case study of 1 patient | Pyridium, 100, 150, or 200 mg t.i.d. | 1 | 73 | F | 3 months |
| Badley, B. W. Brit. Med. J., 2: 850 (1976) | Vol. 1.16 Page: 4760 | Foreign (Canada) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | From age 22 to age 37 | F, W | For up to 3 days on 4 different occasions spanning 15 years |
| Chakraborty, T. K., Filshie, R. J. A. and Lee, M. R. Scot. Med. J., 32: 185-186 (1987) | Vol. 1.16 Page: 4761 | Foreign (Scotland) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 72 | M | Chronic use |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS (Continued)** | | | | | | | | |
| Eisinger A. J., and Jones, R. Lancet, 151, (1969) | Vol. 1.16 Page: 4762 | Foreign (U. K.) | Case study of 1 patient | Pyridium, 200 mg t.i.d. | 1 | 86 | F | 1 month |
| Gabor, E. P., Lowenstein, L., and deLeeuw, N. K. M. Can. Med. Assoc. J., 91: 756-759 (1964) | Vol. 1.16 Page: 4763 | Foreign (Canada) | Case study of 1 patient | Pyridium, 200-600 mg per day , followed by 300 mg per day | 1 | 79 | F, W | 84 days followed by 300 mg per day for 8 days |
| Galun, E., Oren, R., Glikson, M., Friedlander, M., and Heyman, A Drug Intell. Clin. Pharm., 21: 921-922 (1987) | Vol. 1.16 Page: 4764 | Foreign (Israel) | Case study of 1 patient | Pyridium, 400 mg per day occasionally; followed by 1200 mg per day for 3 days | 1 | 29 | F | Occasional use, followed by 1200 mg per day for 3 days |
| **CASE REPORTS OF OVERDOSE OR ABUSE OF DRUG** | | | | | | | | |
| Hood, J. W. and Toth, W. N. J. Amer Med Assoc., 198: 1366-1367 (1966) | Vol. 1.16 Page: 4765 | Foreign (France) | Case study of 1 patient | Pyridium, 100-200 mg t.i.d. | 1 | 25 | F, W | For 1-2 days on 6 different occasions spanning 2 years |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS OF OVERDOSE OR ABUSE OF DRUG (Continued)** | | | | | | | | |
| Alano, F. A., Jr., and Webster, G. D., Jr. Annals of Int. Med., 72: 89-91 (1970) | Vol. 1.16 Page: 4766 | U.S. (Philadelphia, PA) | Case study of 2 patients | Patient #1, Pyridium, 15 mg/kg body wt/day; Patient #2, Pyridium, 500 mg of drug for 4 doses (34 mg/kg body wt) | 1<br>1 | Pt. #1, 75; Pt. #2, 77 | Pt. #1, M; Pt. #2, F | Pt. #1, 5 days Pt. #2, 1 day |
| Cohen, B. L. and Bovasso, G. J. Clin. Pediat., 10: 537-540 (1971) | Vol. 1.16 Page: 4767 | U. S. (Columbus, OH) | Case study of 1 patient | Pyridium, 25-30 tablets of 100 mg each | 1 | 13 months | F, W | One time ingestion |
| Wander, H. J. and Pascoe, D. J. Am. J. Dis. Child., 110: 105-107 (1965) | Vol. 1.16 Page: 4768 | U. S. (Oakland, CA) | Case study of 1 patient | Pyridium, 80 tablets of 100 mg each | 1 | 15 months | F, W | One time ingestion |
| Sand,, R. E., and Edelmann Jr., C. M. J of Pediat., 58:845-846 (1961). | Vol. 1.16 Page: 4769 | U. S. (Portsmouth, VA) | Case study of 1 patient | Amount ingested unknown, empty bottle found | 1 | 3 years | F, W | One time ingestion |
| Bloch, A. and Porter, B. Am J. Dis. Child., 117: 369 (1969) | Vol. 1.16 Page: 4770 | Foreign (Israel) | Case study of 1 patient | Pyridium, 7-8 tablets of 100 mg each | 1 | 18 months | F | One time ingestion |

## TABLE VIII-90 (Continued)

## SUMMARY OF CLINICAL STUDIES WITH PHENAZOPYRIDINE HYDROCHLORIDE

| Investigators, Publications | Full report Data listings | Location | Design | Treatment, Doses | Number enrolled in each treatment | Age (years) | Male/ Female | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| **CASE REPORTS OF OVERDOSE OR ABUSE OF DRUG (Continued)** | | | | | | | | |
| Thomas, R. J., Doddabele, S., and Karnad, A. B. Ann. Intern. Med., 121: 308 (1994) | Vol. 1.16 Page: 4771 | U. S. (Johnson City, TN) | Case study of 1 patient | Abuse of Pyridium, daily dosing equivalent of 4-5 gm | 1 | 43 | F, W | Abuse for several months |

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

# Appendix Six

15 page(s) of revised draft labeling has been redacted from this portion of the review.