

COMMENTS OF  
POLYMEDICA PHARMACEUTICALS ON THE  
REQUEST FOR DATA AND INFORMATION ON THE OVER-THE-COUNTER USE  
OF PHENAZOPYRIDINE HYDROCHLORIDE AS A URINARY TRACT  
ANALGESIC

Docket No. 2003N-0539

June 25, 2004

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Submitted via email to: fdadockets@oc.fda.gov

Comments of Polymedica Pharmaceuticals on the  
Request For Data And Information on the Over-the-Counter Use of Phenazopyridine  
Hydrochloride as a Urinary Tract Analgesic

Docket No. 2003N-0539

Division of OTC Drug Products (HFD-560)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane, Rockville, MD 20857

Dear Sir or Madam:

Polymedica Pharmaceuticals, Inc. submits the following to the Food and Drug Administration (FDA) in response to the agency's request for comments and information regarding over-the-counter (OTC) status of certain drugs. In the Federal Register published on December 31, 2003 (68 Fed. Reg. 75585) (Notice), the Food and Drug Administration (FDA) called for data for certain categories of ingredients in OTC drug products that are eligible for the original OTC drug review but have not been reviewed by FDA to date. Included under the category "Urinary Analgesic/Antiseptic" drug products is the ingredient phenazopyridine hydrochloride. In the Notice, FDA lists eight questions and issues it plans to consider when it evaluates phenazopyridine hydrochloride. FDA invited parties interested in the over-the-counter status of this ingredient to submit their answers to these questions and any supporting data so that this information will be publicly available when FDA reviews this ingredient. The following is Polymedica Pharmaceuticals, Inc.'s first response to the agency's request.

Polymedica Pharmaceuticals has distributed phenazopyridine hydrochloride tablets, 95 mg under the brand name AZO Standard® since December 1992. Prior to that time, Alcon Laboratories, who introduced the product as an over-the-counter drug in 1971, distributed AZO Standard. The information and data outlined below support continued OTC status for phenazopyridine hydrochloride.

## INTRODUCTION

In the Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act, a drug is to be made available without prescription if, by following the labeling,

consumers can use it safely and effectively without professional guidance. Typical questions asked when qualifying a drug product for over-the-counter use include

1. Can the condition be adequately self-diagnosed?
2. Can the condition be successfully self-treated?
3. Is the self-treatment product safe and effective for consumer use, under conditions of actual use?

As demonstrated below, each of the above questions can be answered in the affirmative for phenazopyridine hydrochloride and thus it qualifies for continued use as an OTC drug.

RESPONSES TO QUESTIONS IN THE FEDERAL REGISTER NOTICE (FR DOC.03-32104, PART II.B)

1. Question: Is this condition [urinary pain and discomfort] appropriate for self-medication?

Response: Yes. The symptoms of urinary discomfort include pain, burning, and a frequent and urgent need to urinate. Self-medication for temporary relief of these symptoms is an appropriate over-the-counter indication. The pain and discomfort is readily recognizable and does not require the intervention of a health professional to confirm its presence during urination.

Urinary pain and discomfort are symptoms commonly associated with a urinary tract infection (UTI). Phenazopyridine hydrochloride is a pain reliever and does not treat any underlying infection causing a UTI. As with any other over-the-counter analgesic, the intent of treatment is not to eliminate infection or cure disease but to temporarily relieve pain symptoms.

The labeling of urinary analgesic products clearly instruct the consumer to seek appropriate medical attention if symptoms persist beyond a specific time and also inform the consumer of the limitations of the medications to symptomatic relief.

UTIs can be self-diagnosed using one of several over-the-counter in-vitro diagnostic test kits available to the consumer. Typically these tests use urine dipsticks to detect the presence of nitrites (produced by most bacteria that infect the urinary tract) and/or leukocytes (white blood cells), by a color change on the strip. As part of the FDA 510(k) approval process for home use in-vitro devices, a consumer field evaluation is required to determine that the device performs accurately when used by lay users, unassisted, following instructions provided in the labeling.<sup>1</sup> Examples of devices that have received 510(k) approval by FDA's Center for Devices and Radiological Health are listed below:

<u>Device Name</u>	<u>510(k)</u>
Biotel / UTI	K855238
Urine Diagnostic Reagent Strips	K862806
First Choice Urinary Tract Infection Test Strips	K953672
Uritest – Nitrite in Urine Test	K954685
Chek-Stix U.T.I Self-Test	K960888
Dbest Urinary Tract Infection Kit for Home Use	K990873

In most cases where a UTI is diagnosed, a physician prescribes antibiotics that kill the bacteria that cause UTIs. Phenazopyridine hydrochloride provides the consumer with effective, interim relief from the pain and burning associated with a UTI while waiting to see their doctor for diagnosis and treatment, or waiting for a prescription to take effect.

The FDA has determined that internal analgesics are suitable for self-medication of occasional minor headaches, reduction of fever and to alleviate the symptoms of “mild to moderate” aches and pain. “Mild to moderate” pain for the purposes of self-medication may be defined as pain that is self-limited and which requires no special treatment or prior diagnosis by a physician. Analgesics alleviate pain principally by a peripheral effect (blockade of pain impulse generation) rather than by central effect. Phenazopyridine hydrochloride provides relief of mild to moderate pain. Phenazopyridine hydrochloride provides the consumer with effective, interim relief from the pain and burning associated with a UTI. The pain/discomfort associated with a UTI is characterized as mild to moderate, self limited and requires no special treatment or prior diagnosis by a physician, thus meeting the OTC analgesic requirements set forth by the FDA in the Advanced Notice of Proposed Rulemaking published on July 8, 1977 (42 FR 35346-35621).

2. Question: If the answer to the first question is yes, should the product labeling mention the possible need for treatment with an antibacterial drug also?

Response: No. The current labeling requirements are sufficient to ensure safe and effective use of phenazopyridine hydrochloride by consumers. The DESI notice published in the Federal Register of July 29, 1983 (48 Fed. Reg. 34516) announced certain required labeling for phenazopyridine-containing drug products indicated for use in relieving symptoms often associated with a urinary tract infection including:

“...in its dosage and dosing interval recommendations pertaining to the use of the product in urinary tract infections, the DOSAGE and ADMINISTRATION section shall show that the product is only indicated for up to 2 days (the effect of phenazopyridine hydrochloride should not be relied upon after 48 hours).”

The labeling should not suggest a specific mode of treatment (e.g., antibacterial). Proper treatment needs to be determined after diagnosis by a healthcare professional.

Examples of urinary analgesic product labeling that clearly instruct the consumer to seek appropriate medical attention if symptoms persist beyond a specific time found on currently marketed products include:

“Do not use for more than 2 days (12 tablets) without consulting a doctor,”

“Do not exceed 12 tablets per course of treatment. If symptoms persist, please contact a healthcare professional”

3. Question: Is there a valid basis for having single-ingredient prescription products with a 200 mg dose and over-the-counter products with a 190 to 195 mg dosage? What data support these dosages?

Response: Use of phenazopyridine as a urinary analgesic can be traced as far back as 1925 with the establishment of the Pyridium Corporation<sup>2</sup>. Phenazopyridine hydrochloride has over-the-counter marketing status based on the ingredient’s extensive marketing history in the United States that predates the 1951 Durham-Humphrey Amendments to the Federal Food, Drug, and Cosmetic Act.

The agency standard for effectiveness for an over-the-counter drug is that there is a reasonable expectation that when the drug is used by consumers as an over-the-counter product (without professional supervision, but with adequate directions for use and warnings against unsafe use), the drug will provide a clinically significant benefit of the type claimed in the labeling, for a significant proportion of the consumers who use the product.<sup>3</sup>

Although we are not aware of any specific clinical dosage studies, phenazopyridine hydrochloride has a long history of OTC use. A review of literature including the FDA Safety Information and Adverse Event Reporting Program (MedWatch) indicates the absence of any evidence of adverse events at this dosage. In addition, our complaint handling system requires the reporting of serious adverse events in compliance with Code of Federal Regulations for Food and Drugs (21 CFR 310.305 and 21 CFR 314.80) and we have had no adverse events reported. Together, these facts indicate that phenazopyridine hydrochloride dosages of 190 to 195 mg. are safe and effective.

NOTE: Response to Questions #4 - #7 combined below following #7

4. Question: Have epidemiological studies been done since 1978 that address the neoplasia findings in the National Cancer Institute technical report?
5. Question: Are the neoplasia findings of sufficient concern to restrict this drug to prescription status?
6. Question: Do consumers adequately understand the required carcinogenesis labeling statement?
7. Question: Should the carcinogenesis labeling statement be required to appear on the outer package labeling, or is it adequate that it appear only in a package insert?

Response: There is insufficient evidence to require a carcinogenesis labeling statement on products containing phenazopyridine hydrochloride.

The current carcinogenesis labeling statement required by FDA is based on animal studies (rats and mice), where long term, high dose exposure to phenazopyridine hydrochloride induced neoplasia. The negative results of the 1978 epidemiological study found no association between the use of phenazopyridine hydrochloride and human neoplasia. The exposure conditions giving rise to the positive results in these animal studies lack relevance to conditions of either prescription or over-the-counter use. Data from these studies cannot be interpreted to demonstrate a significant human health risk.

In an epidemiological study of 2,214 patients who received phenazopyridine hydrochloride and were followed for three years, no significant excess of any cancer was observed (IARC 1987).

FDA has long recognized that over-the-counter labeling should be based on scientific evidence and that warnings should be instructional and actionable. Under FDA's established over-the-counter labeling policy, label warnings are appropriate only for significant human health risks that are scientifically documented. The agency's own regulations articulate this policy:

Warning statements for over-the-counter drug products should be limited to those that are scientifically documented, clinically significant, and important for the safe and effective use of the products by consumers.<sup>4</sup>

Inclusion of the carcinogenesis statement in the product labeling is inconsistent with the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 201(n) of the Act, a product's label must disclose "material" information about the consequences of using the product. This does not require disclosure of everything that is known or being investigated about a product. In promulgating its regulation interpreting the "materiality" standard of section 201(n), FDA explained that a warning is

justified under the section only if “reasonable evidence exists indicating as association between a drug and a serious hazard.”<sup>5</sup>

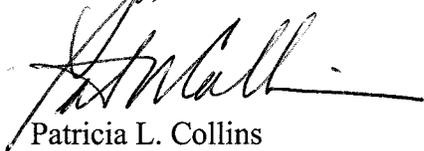
The required reference to the potential cancer risk supposedly associated with phenazopyridine hydrochloride would suggest that cautionary labeling should be required every time the agency is faced with investigating an unestablished chronic risk that theoretically may be related to a product. Pursuit of this strategy would lead to a plethora of scientifically unsubstantiated and confusing label warnings on drugs, and perhaps foods as well.

Finally, the carcinogenesis warning is counterproductive. Rather than providing useful, practical and definitive guidance to consumers as to how, when and if they should use that product and/or consult their doctors, the labeling disseminates ambiguous, misleading, and potentially frightening information concerning which the consumer has little ability to make an informed decision and could deter a consumer from seeking relief.

8. Issue: Provide updated safety data both from the literature and from adverse event reports for the last 20 years, especially those adverse events reported to companies that market these products.

Response: A review of literature including the FDA Safety Information and Adverse Event Reporting Program (MedWatch) indicates the absence of any evidence of adverse events. Since we began distribution in December 1992, we have sold approximately 11 million packages of AZO Standard®. Our complaint handling system requires the reporting of serious adverse events in compliance with Code of Federal Regulations for Food and Drugs (21 CFR 310.305 and 21 CFR 314.80) and we have had no adverse events reported.

Sincerely,



Patricia L. Collins  
Director, QA/QC and Regulatory Affairs  
PolyMedica Pharmaceuticals, Inc.

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<sup>1</sup> Points to Consider Regarding Labeling and Premarket Submissions for Home-Use In Vitro Diagnostic Devices [http://www.fda.gov/cdrh/manual/ivdapp.html#appendix\\_C](http://www.fda.gov/cdrh/manual/ivdapp.html#appendix_C)

<sup>2</sup> <http://www.rutherfordchemicals.com/nepera.html>

<sup>3</sup> Questions and Answers Over-the-Counter Drug Products Public Hearing June 28-29, 2000 (<http://www.fda.gov/cder/meeting/otcqa-600.html>)

<sup>4</sup> 53 Fed Reg 46204, 46213 (November 16, 1988)

<sup>5</sup> 40 Fed. Reg. 25852, 25853 (July 1975)