



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 18 2002

Howard R. Udell
Executive Vice President
The Purdue Frederick Company
1 Stamford Forum
Stamford, Connecticut 06901-3431

Re: Docket Nos. 82N-0291/CP, 80N-0476
and 75N-0183

Dear Mr. Udell:

This is in response to your company's citizen petition dated December 16, 1988, which was filed on December 23, 1988 as Comment No. CP under Docket No. 82N-0291 in FDA's Dockets Management Branch. The petition requested the reopening of the administrative record for the advance notice of proposed rulemaking (ANPR) for over-the-counter (OTC) vaginal drug products, published in the FEDERAL REGISTER of October 13, 1983 (48 FR 46694), to include further comments and supporting data for the use of povidone-iodine formulations (solutions, gels, and suppositories) at a 10 percent concentration for the symptomatic relief of minor vaginal irritation and itching, and to permit health professionals to recommend these formulations for more "defined clinical conditions". The petition stated that 10 percent povidone-iodine formulations offer convenient alternative products to the consumer, provide safe and effective relief of minor symptoms of vaginal irritation and itching, and permit health professionals to recommend these formulations for more "defined clinical conditions". Your petition included published and unpublished reports containing data on safety and efficacy, adverse drug reactions, side effects, labeling, and formulations to support your position.

In the ANPR (48 FR 46694 at 46728), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Panel) classified povidone-iodine in a concentration of 0.15 to 0.30 percent as safe and effective (Category 1) when used as an OTC vaginal douche for the relief of minor vaginal itching, irritation, and soreness. The Panel recommended professional labeling indications for the treatment of vaginal moniliasis, *Trichomonas vaginales*, and non-specific vaginitis (48 FR 46994 at 46729). This treatment regimen includes the use of the dilute douche combined with the application of the full-strength (10 percent) povidone-iodine to the vaginal mucosa. The Agency has not yet published a tentative final monograph on povidone-iodine for the relief of minor vaginal itching and irritation or for any professional labeling claims.

The Division of OTC Drug Products (the Division) has reviewed the data and information

80N-0476

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submitted in your petition for consideration of 10 percent povidone-iodine formulations for the relief of minor vaginal irritation and itching, or for relief of minor vaginal soreness. You mentioned that clinical effectiveness of povidone-iodine preparations was evaluated in four studies, summarized below, involving approximately 270 subjects.

1. (Ref. 1. Double-blind multi-investigator clinical and microbial evaluation of Betadine Vaginal Gel (BVG) in the treatment of monilial vaginitis. Study No. 1208, included in Comment No. CP, Docket No. 82N-0291, Dockets Management Branch):

This summary of an unpublished study reported the results of a double-blind, multi-investigator clinical and microbiological evaluation of Betadine Vaginal Gel (BVG) vs. Mycostatin Vaginal Tablets for the treatment of monilial vaginitis. This study involved 135 women who used either BVG (N=66) or Mycostatin (N=69) once daily for two weeks. The summary of the data stated that 39 of 46 (85 percent) evaluable subjects in the BVG treated group reported first improvement in symptoms within the first 7 days of treatment and 35 of 66 (53 percent) evaluable subjects reported complete improvement in symptoms within the first 7 days of therapy. The Mycostatin treated group showed similar results. One subject receiving the povidone-iodine gel withdrew from the study after 2 days with redness, edema, and pain. Another subject reported severe burning during days 10- 14 of treatment. One Mycostatin treated patient reported vulvar burning.

2. (Ref. 2. A multi-investigator open label safety and efficacy study of Betadine Antiseptic Gel in patients with minor vaginal soreness, irritation and itching. Study No. 84-0705, included in Comment No. CP, Docket No. 82N-029 1, Dockets Management Branch):

This summary of an unpublished, multi-investigator, open label safety and efficacy study of Betadine Antiseptic Gel involved 36 women with minor vaginal soreness, irritation, and/or itching who used it once daily for 1 week. The summary stated that usage resulted in total or partial relief of 99 percent of these complaints (86 percent totally relieved and 13 percent partially relieved) with minor incidence of irritation (three subjects reported burning and one reported stinging at the first application; one subject discontinued therapy because of adverse events of uncertain relationship to drug treatment).

3. (Ref. 3. An open label safety and efficacy study of Betadine Vaginal Suppositories in patients with minor vaginal soreness, irritation and itching. Study No. 85-0201, included in Comment No. CP, Docket No. 82N-0291, Dockets Management Branch):

This summary of an unpublished, open label, safety and efficacy study of Betadine Vaginal Suppositories (BVS) involved 40 women with minor vaginal soreness, irritation, and/or itching who received treatment once daily for 1 week. The summary stated that usage resulted in total or partial relief of 97 percent of these complaints (81 percent totally relieved and 16 percent partially relieved) with minor incidence of irritation (one complaint of persistent irritation and

one complaint of itching which remained unchanged during the course of treatment). Two subjects reported burning at the first application, which was not reproduced at subsequent applications.

4. (Ref. 4. Beaton, J.H., F. Gibson, and M. Roland, "Short-term Use of a Medicated Douche Preparation in the Symptomatic Treatment of Minor Vaginal Irritation, in Some Cases Associated with Infertility." *International Journal of Fertility*. 29(2):109-112, 1984):

This published study reported on the treatment of the symptoms of minor vaginal irritation of unknown etiology in 56 women using a disposable 0.25 percent povidone-iodine douche preparation in a 1-week trial. The investigators concluded that 50 subjects (89.3 percent) were completely cleared of the signs and symptoms of vaginal irritation and 5 subjects (8.9 percent) obtained partial relief.

Our review of the submitted data described above finds that the information is incomplete and insufficient to support the safety and effectiveness of the 10 percent povidone-iodine formulations for the relief of minor vaginal irritation and itching, or for relief of minor vaginal soreness. Three out of the four studies (Refs. 1-3) were unpublished and conducted by the applicant. Only study summaries were submitted. Details are lacking regarding the subject population used, selection criteria, criteria for blinding, controls, clinical diagnosis, data collection, microbiological measurements and results, criteria for symptom relief, measurement of symptom relief, statistical analysis, etc. In the Beaton et al. study (Ref. 4), the medicated douche solution used contained 0.25 percent povidone-iodine and not the 10 percent povidone iodine that was requested by the petition. Therefore, this study cannot be used in support of 10 percent povidone-iodine for treating the symptoms of minor vaginal irritation and itching.

Furthermore, the Panel (48 FR 46694 at 46728) has already recommended the 0.15 to 0.30 percent concentrations for relief of minor vaginal irritation and itching.

The Division finds that no rationale has been provided for the use of the higher 10 percent concentration for treating the same symptoms that can be treated with the 0.15 to 0.30 percent povidone-iodine formulations. In the interest of safety, the lowest possible effective dosage (i.e., 0.15 to 0.30 percent) should be used. The Division finds that your petition, in support of 10% povidone-iodine formulations for the relief of minor vaginal irritation and itching, or for relief of minor vaginal soreness, does not contain an adequate clinical safety database generated from large enough numbers of subjects from adequate and well controlled studies to clarify its safety profile. Adequate safety and effectiveness data, as well as a rationale to support the 10 percent concentration, are needed to include 10 percent povidone-iodine (solutions, gels, and suppository dosage forms) in the monograph for relief of symptoms of minor vaginal irritation and itching. We also refer you to the April 15, 1997 meeting of the Nonprescription Drugs Advisory Committee (with representation from CDER's Reproductive Health Drugs and Anti-infective Drugs Advisory Committees) in which the association between vaginal douching and adverse consequences, such as pelvic inflammatory

disease (PID), ectopic pregnancy, and cervical cancer, was discussed. Although the Advisory Committee felt that more data are needed to support an association between PID and douching, they thought that douching could promote PID in those women prone to it. The Committee also recommended consistent, easy to understand labeling for vaginal douche products, particularly in regard to when consumers should seek medical advice after the onset of symptoms.

The Division also concludes that the data are inadequate to support the use of 10 percent povidone-iodine formulations (solutions, gels, and suppositories) for professional labeling for the treatment of vaginal moniliasis, *Trichomonas vaginales*, and non-specific vaginitis. The same data to support the use of 10 percent povidone-iodine for relief of symptoms of minor vaginal irritation were also submitted to support use of 10 percent povidone-iodine for the professional labeling claims. Thus, the deficiencies of the studies described above for 10 percent povidone-iodine for the relief of minor vaginal irritation, itching, or minor vaginal soreness apply also for the requested professional labeling claims. Further, we have re-evaluated the studies reviewed by the Panel and disagree with the Panel's recommendations (48 FR 46694 at 46705-46706) to include professional labeling claims for a treatment program using povidone-iodine as a microbicidal douche and as a treatment for vaginal moniliasis, *Trichomonas vaginitis*, and non-specific vaginitis. We find that the data relied upon by the Panel do not provide sufficient evidence of effectiveness for these claims.

In 1990, the Fertility and Maternal Health Drugs Advisory Committee recommended that topical vaginal antifungals be allowed to be sold OTC because they felt that consumers could recognize and treat candidiasis after initial professional diagnosis. Thus, the treatment of vaginal candidiasis (moniliasis) is currently allowed as an OTC condition under an approved new drug application (NDA). Therefore, the professional labeling claims for povidone-iodine recommended by the Panel in § 351.180 will not be proposed in other OTC drug monographs. We recommend submission of safety and efficacy data under an NDA for professional labeling claims. Such an application must also include adverse event reports from all marketed povidone-iodine vaginal douche products (US and foreign).

In conclusion, we have determined that the data submitted do not support a Category I classification for the 10 percent povidone-iodine formulations (solutions, gels, and suppositories) for the relief of minor vaginal irritation and itching, nor do the data reviewed by the Panel or included in your petition support the professional labeling claims proposed by the Panel in § 351.180 (48 FR 46694 at 46729). As stated above, we conclude that there are no supporting data to use the higher 10 percent concentration to treat the same symptoms (relief of minor vaginal itching and irritation) that can be treated with the 0.15 to 0.30 percent povidone-iodine formulations.

For the reasons stated above, the Agency is denying your petition.

As you are aware, the Agency published a notice of withdrawal of the advance notice of proposed rulemaking for OTC vaginal drug products on February 3, 1994 (59 FR 5226). Therefore, any comment you may wish to make on the above information should be identified with the appropriate Docket No. (80N-0476 for Topical Antifungal Drug Products or 75N-0183 for Topical

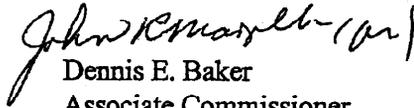
Howard R. Udell

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Antimicrobial Drug Products) and submitted in three copies to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,



Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5-16-02

FROM: Director
Division of OTC Drug Products, HFD-560
82N-0291/CP

SUBJECT: Material for Docket No. 80N-0476; 75N-0183

TO: Dockets Management Branch, HFA-305

The attached material should be placed on public display under the above referenced Docket No.

This material should be cross-referenced to Comment No. _____


Charles J. Ganley, M.D.

Attachment