DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

21 CFR Part 310
[Docket No. 82N-0168]

Drug Products To Treat the Symptoms of Benign Prostatic Hypertrophy for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would classify over-the-counter (OTC) drug products to treat the symptoms of benign prostatic hypertrophy (enlarged prostate gland) as not generally recognized as safe and effective and as being misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by December 30, 1982 and reply comments by January 31, 1983.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on August 23, 1981 a statement on OTC drug products to treat the symptoms of benign prostatic hypertrophy from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC drug products to treat the symptoms of benign prostatic hypertrophy are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The Panel's recommendations on OTC drug products to treat the symptoms of benign prostatic hypertrophy contain no Category I or Category III conditions, and FDA is issuing the Panel's recommendations proposing Category II classification of OTC drug products to treat the symptoms of benign prostatic hypertrophy.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The statement has been prepared independently of FDA, and the agency has not yet fully evaluated the statement. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendation that OTC drug products to treat the symptoms of benign prostatic hypertrophy be classified as Category II. If the agency proposes to adopt the Panel's recommendations, a regulation declaring these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR Part 310, Subpart E). The agency is including, in this advance notice of proposed rulemaking, a regulation based upon the Panel's recommendations in order to obtain full public comment at this time.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a proposed rulemaking on OTC drug products to treat the symptoms of benign prostatic hypertrophy. The agency's position on OTC drug products to treat the symptoms of benign prostatic hypertrophy will be stated initially when that notice of proposed rulemaking is published in the **Federal Register**. In the notice of proposed rulemaking, the agency will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part . (proposed in the **Federal Register** of December 11, 1979; 44 Fr 71742).

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products to treat the symptoms of benign prostatic hypertrophy. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC drug products to treat the symptoms of benign prostatic hypertrophy should be accompanied by appropriate documentation.

If FDA proposes to adopt the Panel's recommendations, the agency will propose that the final rule for OTC drug products to treat the symptoms of benign prostatic hypertrophy be effective 6 months after its date of publication in the **Federal Register**. Because benign prostatic hypertrophy is not a self-diagnosable disorder, and OTC treatment might unnecessarily delay diagnosis and treatment of a prostatic malignancy, the agency believes 6 months to be a reasonable effective date for the final rule. On or after the effective date of the final rule no OTC drug products that are subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information generated by the agency and considered by the Panel concerning OTC drug products to treat the symptoms of benign prostatic hypertrophy. This information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after November 1, 1982, except to the extent that its content falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)).

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR

9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient'.") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of ingredients in miscellaneous internal drug products to be considered in the OTC drug review. The list, which did not include ingredients for the treatment of the symptoms of benign prostatic hypertrophy, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973 and August 27, 1975 informed OTC drug product manufacturers of the opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a)(1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal drug products:

James L. Tullis, M.D., Chairman (appointed December 1979)
John W. Norcross, M.D., Chairman (resigned March 1979)
Diana F. Rodriquez-Calvert, Pharm. D. (appointed July 1976)
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D. (deceased June 1, 1981)
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D., Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R. Ph., served as the Panel Administrator until July 1979, followed by John R. Short, R.Ph. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for OTC drug products to treat the symptoms of benign prostatic hypertrophy in this document. The Panel's findings on other categories of miscellaneous internal drug products are being published periodically in the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. The only meeting at which drug products to treat the symptoms of benign prostatic hypertrophy were discussed was held on August 23, 1981.

The minutes of that Panel meeting are on public display in the Docket Management Branch (HFA-305), Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss OTC drug products to treat the symptoms of benign prostatic hypertrophy, nor was any individual requested to appear by the Panel.

Although no submissions were received, the Panel thoroughly reviewed information prepared by FDA in arriving at its conclusions and recommendations for OTC drug products to treat the symptoms of benign prostatic hypertrophy.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC drug products to treat the symptoms of benign prostatic hypertrophy with respect to the following three categories:

Category I. Conditions under which OTC drug products to treat the symptoms of benign prostatic hypertrophy are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC drug products to treat the symptoms of benign prostatic hypertrophy are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel considered three active ingredients (glycine, alanine, and glutamic acid) in OTC drug products to treat the symptoms of benign prostatic hypertrophy and classified these ingredients in Category II.

The "OTC Volume" cited in this document contains material prepared by the agency. All of the information included in this volume, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display following publication of this statement in the **Federal Register**, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Statement by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products on OTC Drug Products to Treat the Symptoms of Benign Prostatic Hypertrophy

The Panel completed a review of ingredients to treat the symptoms of benign prostatic hypertrophy and offers the following general information.

A benign overgrowth of the prostate is a relatively common accompaniment to aging in males. The cause is unknown, but evidence suggests it is secondary to hormonal imbalance. About 50 percent of all men over the age of 50 develop some clinical evidence of the disease, and, of these, approximately 10 percent

require sugical intervention. The growth is characterized principally by an abnormal increase in the number of cells leading to a benign swelling with some normal glandular prostatic tissue still being present. The size of the growth may amount to from 1 to 10 times the normal prostatic weight. The resulting symptoms include urinary frequency, nocturia, difficulty in initiating voiding, and, in rare instances, complete bladder outlet obstruction. Although there is no direct relationship between benign prostatic hypertrophy and adenocarcinoma of the prostate, there are similarities between the two conditions. Adenocarcinoma of the prostate also occurs primarily in men over the age of 50 and produces the same obstructive symptoms. This malignant disease occurs in approximately 15 percent of men in their fifties and as many as 60 percent of men in their eighties. It is a major cause of death from malignancies in males, accounting for some 10 percent.

It is possible for prostatic carcinoma to be present concurrently with benign prostatic hypertrophy or to be confused with it. Blood tests, such as the serum acid phosphatase, help to diagnose prostatic carcinoma if the growth is beyond the capsule of the prostate, but in the early stages a hard nodule that indicates its prsence may be detected only by rectal palpation. Thus, any treatment of prostatic enlargement by OTC drugs might unnecessarily delay diagnosis and treatment of a malignancy.

The agency is aware of three products marketed OTC for the treatment of symptoms of benign prostatic hypertrophy. Each of these products contains a mixture of three amino acids, glycine, alanine, and glutamic acid and has been marketed for many years. Initial marketing of these products for this use presumably was based on the observation of improvement in a patient in Boston who originally took the mixture for another reason and noted improvement in his urinary difficulty. There is no evidence to show any potential harm from ingestion of these three naturally occurring amino acids, but, as mentioned above, there is a danger that the symptoms being treated are the result of prostatic cancer rather than benign hypertrophy.

A package insert accompanying one of these OTC drug products describes four studies purporting to show the effectiveness of the product (Ref. 1). The first study, involving 50 men in the Boston area, showed that the product provided relief in 80 percent of the cases. About 3 years after this study, a separate follow-up field study questionnaire on 100 men revealed that ". . . a large majority had received relief ranging from fair to excellent within a very few weeks." Two more studies, conducted in New York City during the 1950's, found that 80 percent of one group of 40 men ". . . secured substantial relief from their symptoms of Benign Prostatic Hypertrophy" and another 40 had ". . . very good results." Because of the subjective nature of the described results, the Panel concludes that these studies do not provide valid support of effectiveness.

In 1962 the U.S. District Court in Massachusetts granted a permanent injunction against the manufacturer of the products mentioned above on the basis of misbranding (Ref. 1). This prohibited the interstate distribution of these products at that time, but the manufacturer revised the labeling and the products once again were marketed over-the-counter. In granting the injunction, the Court stated that "a fair interpretation of their literature, of which 15 samples are attached to the complaint, would indicate to the lay mind that the use of [trade name] can be a substitute for surgery in the treatment of prostatic disorders."

The Panel Chairman solicited information about one of these products from two prominent urologists in the Boston area (Ref. 1). Both believed there was no rational reason why amino acids would alter the obstructive or inflammatory signs and symptoms of benign prostatic hypertrophy. A review of the *Journal of Urology* Index from 1948 included no mention of the product.

The Panel is not aware of any definitive clinical trials with appropriate controls, nor is there any a priori basis for assuming the effectiveness of these ingredients. The Panel, therefore, recommends that the mixture of amino acids the products contain be placed in Category II for safety and effectiveness. Because benign prostatic hypertrophy cannot be self-diagnosed and because OTC treatment might unnecessarily delay diagnosis and treatment of a prostatic malignancy, the Panel concludes that no ingredient or mixture of ingredients should be available OTC to treat the symptoms of this condition.

Reference

(1) OTC Volume 170233.

List of Subjects in 21 CFR Part 310

New drugs.

PART 310—NEW DRUGS

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 310 by adding to Subpart E new § 310.532, to read as follows:

§ 310.532 Drug products containing active ingredients offered over-the-counter (OTC) to treat the symptoms of benign prostatic hypertrophy.

(a) Glycine, alanine, and glutamic acid (in combination) have been marketed to treat the symptoms of benign prostatic hypertrophy. There is a lack of adequate data to establish the safety and effectiveness of these, or any other, ingredients for treating the symptoms of this disorder. In addition, benign prostatic hypertrophy is not a self-diagnosable disorder, and OTC treatment might unnecessarily delay diagnosis and treatment of a prostatic malignancy. Therefore, any OTC drug product containing ingredients offered to treat the symptoms of benign prostatic hypertrophy cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted to treat the symptoms of benign prostatic hypertrophy is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC to treat the symptoms of benign prostatic hypertrophy is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Interested persons may, on or before December 30, 1982, submit to the Dockets Management Branch (HFA-

305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before January 31, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: September 22, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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