DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 82N-0168]

RIN 0905-AA06

Benign Prostatic Hypertrophy Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any benign prostatic hypertrophy drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective and is misbranded. Benign prostatic hypertrophy drug products are used to relieve the symptoms of an enlarged prostate gland. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on benign prostatic hypertrophy drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 27, 1990.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43566), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that (1) would classify OTC benign prostatic hypertrophy drug products as not generally recognized as safe and effective and as being misbranded and (2) would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by December 30, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 31, 1983.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC benign prostatic hypertrophy drug products, was published in the **Federal Register** of February 20, 1987 (52 FR 5406). Interested persons were invited to file by April 21, 1987, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by June 22, 1987. New data could have been submitted until February 22, 1988, and comments on the new data until April 20, 1988. Final agency action occurs with the publication of this final rule on OTC benign prostatic hypertrophy drug products.

In the preamble to the agency's proposed rule on OTC benign prostatic hypertrophy drug products (52 FR 5406), the agency stated that no benign prostatic hypertrophy active ingredient had been found to be generally recognized as safe and effective and not misbranded, but that Category I labeling was being proposed in that document in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status in the final rule. In this final rule, no benign prostatic hypertrophy ingredient has been determined to be generally recognized as safe and effective for use in OTC drug products intended for relieving the symptoms of benign prostatic hypertrophy. Therefore, proposed 21 CFR part 357, Subpart L for OTC benign prostatic hypertrophy drug products is not being issued as a final regulation.

This final rule declares OTC drug products containing active ingredients for benign prostatic hypertrophy use to be new drugs under section 201(p) of the act, for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing these drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing active ingredients for relieving the symptoms of benign prostatic hypertrophy by adding to subpart E new § 310.532 (21 CFR 310.532). The inclusion of OTC benign prostatic hypertrophy drug products in part 310 is consistent with FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, and 310.533.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC benign prostatic hypertrophy drug product, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

In the proposed rule for OTC benign prostatic hypertrophy drug products (52 FR 5406), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of benign prostatic hypertrophy drug products to be in compliance with the monograph. Although one manufacturer submitted data and information in response to the proposed rule, the data and information were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, benign prostatic hypertrophy drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking (47 FR 43566), the agency stated that if it proposed to adopt the Panel's recommendations that OTC drug products to treat the symptoms of benign prostatic hypertrophy are not generally recognized as safe and

effective and are misbranded, it would propose that these drug products be eliminated from the OTC market effective 6 months after the date of publication of a final rule in the **Federal Register**. Therefore, because the agency is now adopting the Panel's recommendations and no OTC drug monograph is being established for this class of drug products, on or after August 27, 1990. No OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of this final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

In response to the proposed rule on OTC benign prostatic hypertrophy drug products, one manufacturer submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch. Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

One manufacturer submitted several animal, in vitro, and clinical studies in support of the safety and effectiveness of the liposterolic extract of sabal for relieving the symptoms of benign prostatic hypertrophy (Ref. 1). The manufacturer also provided a number of references on the historical use of the parent plant sabal (serenoa serrulata or serenoa repens) and stated that sabal has a long history of safe and effective use for this indication (Ref. 2).

The agency recognizes that, in the past, sabal was an official article in the *United States Pharmacopoeia*, 1905 to 1926 (Refs. 3 and 4) and *The National Formulary*, 1926 to 1950 (Refs. 5 through 8). It was also listed in *The Physicians' Desk Reference*, 1948 (Ref. 9) and *Remington's Practice of Pharmacy* (Ref. 10). Currently, it is listed in the *Homoeopathic Pharmacopoeia of the United States*, 1979 (Ref. 11). The agency acknowledges that these historical references show that sabal has been prescribed in the past for urgency, frequency of urination, and excess night urination associated with inflammation of the bladder and enlargement of the prostate gland. It also has been used as a nutritive tonic, in respiratory diseases and digestive disturbances, and as a mild diuretic and sedative in cystitis (Refs. 9, 12, and 13).

The agency has reviewed the animal and in vitro studies submitted and concludes that, while supportive, they are inadequate to establish that the liposterolic extract of sabal is generally recognized as safe and effective as an ingredient in OTC drugs intended for the treatment of the symptoms of benign prostatic hypertrophy. These studies primarily contain data and information on the mode and mechanism of action of the liposterolic extract of sabal. While such information is useful, the studies provides no evidence to establish the effectiveness in humans of OTC benign prostatic hypertrophy drug product ingredients.

In the two human clinical studies submitted, the liposterolic extract of sabal appears to be safe for short-term use. However, the clinical studies do not provide sufficient evidence of effectiveness, i.e., adequate and meaningful clinical improvement to support a labeling claim and the establishment of a monograph for drug products intended to be used for relieving the symptoms of benign prostatic hypertrophy.

The first clinical study is a double-blind, randomized, placebo-controlled clinical trial by Champault et al. (Ref. 14), in which 110 patients with prostatic adenoma were either given the placebo or 320 milligrams (mg) per day (two 80-mg tablets twice per day) of the liposterolic extract of sabal, identified as PA 109. Patients valid for surgery were excluded. In the final assessment, 88 patients (41 in the placebo group and 47 in the treatment group) were included in the study. Efficacy was assessed after 1 month. The objective criteria used were nocturnal frequency, urinary output, and residual urine. The subjective criteria used were dysuria and the patients' opinions. At baseline, the treatment and placebo groups were found to be comparable for each of the parameters assessed. Reported results of the study suggest that patients treated with PA 109 showed a statistically significant improvement, demonstrating an increase in the mean urine volume from 5.35 to 8.05 milliliters per second (mL/sec), reduction in the residual urine from 94.7 to 55.05 mL, and a decrease in the mean number of nocturnal micturitions (night urinations) from 3.12 to 1.69. No statistically significant difference was reported for the placebo for any of the parameters assessed. The placebo group showed only a slight change for the mean urine volume (5.04 to 5.29 mL/sec), the residual urine (91.3 increased to 100 mL), and the mean number of nocturnal micturitions (3.12 to 2.7). The difference between the placebo and treatment groups for all parameters assessed were reported as statistically significant for all values given to extent of less than 10^{-9}.

Although the Champault study suggests that patients treated with PA 109 showed some statistical improvement in the symptoms associated with benign prostatic hypertrophy, the results are not considered clinically significant, i.e., the symptoms continue to exist and the patient is not medically better. The decrease with PA 109 in the mean number of nocturnal micturitions from 3.12 to 1.69, compared to 3.12 to 2.7 for the placebo, may be statistically significant; however, the reduction represents a decrease of actually only 1 micturition, which the agency does not consider to be clinically significant. The reduction in the residual urine from 94.7 to 55.05 mL also appears statistically significant. However, a residual urine value above 50 mL still suggests some obstruction or abnormality of the bladder, possibly secondary to urethral obstruction (Ref. 15) because Hinman and Cox found that the mean volume of residual urine in normal male subjects appears to be 0.53 mL (Ref. 16). Because the resultant residual urine volume values in the study are much higher than the normal population, the reported 55.05 mL results do not indicate a clinically meaningful improvement.

During the course of the Champault study, a long-term open study on tolerance and efficacy was also conducted. The mean assessment period was 14.6 months, ranging in total between 7 and 30 months. The authors initially report that 47 patients received treatment with PA 109, but later indicated that 32 of the 47 patients received treatment with PA 109 and 15 patients received treatment with the placebo. The authors further report that, at 6 months, traces were lost on 3 patients; 4 had been operated on for the condition, and 40 retained a good therapeutic effect. Results reported after 1 year indicate that 37 of the 40 remaining patients available to followup had improved symptoms and efficacy of treatment had remained intact. However, it is not clear from the authors' description of this open study how many of the study participants were in the treatment group and how many were in the placebo group. Because of the inconsistencies of details and inadequate information, no further

assessment of this phase of the study can be made.

The second study by Tasca et al. (Ref. 17) was also double-blind, randomized, and placebo-controlled. In this study, 30 patients with prostatic adenoma in stages I and II were randomly subdivided into two groups and given either placebo or 320 mg of PA 109 in two doses of 160 mg each. The exact length of the study was not given. Of the 30 patients, 27 finished the study. Thus, the evaluation refers to 14 patients treated with PA 109 and 13 treated with placebo. Urinary and uroflowmetric symptomatic data were obtained on each patient before and after treatment and indicate statistical significance for PA 109 when compared to the placebo. The investigators reported that subjective analysis of the results indicated that good results were obtained in 42 percent of patients who received PA 109, while only 15.4 percent of patients who received placebo were rated as "good." Patients treated with PA 109 showed an increase in the mean urine volume from 4.9 to 7.9 mL/sec, an increase in urine flow rate from 12.9 to 16.2 mL/sec, and an increase in volume emptying from 248 to 296 mL. However, an increase in flow rate of 12.9 to 16.2 mL/sec may represent only a slight improvement in clinical symptoms. Normally, males deliver a urine flow rate of 20 to 25 mL/sec. Any flow rate below 15 mL/sec is highly suggestive of obstruction or dysfunction (Refs. 18 and 19). Thus, a flow rate of 16.2 represents only minimal improvement, and the agency does not consider this to be clinically significant.

Champault et al. (Ref. 14) and Tasca et al. (Ref. 17) appear to be small well-controlled clinical trials with some evidence of statistical significance of PA 109 over the placebo. The results of these studies appear to suggest that PA 109 may be useful in providing minimal relief of the symptoms of benign prostatic hypertrophy. The data suggest that the drug probably has an effect that minimally improves the ability to empty the bladder and minimally improves the symptoms of outlet obstruction. However, the agency concludes that the change shown for "before treatment" and "after treatment" with PA 109 in these studies does not reflect an adequate or meaningful clinical improvement for the treatment of the symptoms of benign prostatic hypertrophy. Because the efficacy parameters show only minimum improvement in the treatment groups, the agency considers the results of these studies inadequate to establish effectiveness. Also, there were too few participants in these studies to support general recognition of effectiveness for PA 109. Additional studies are needed with an adequate number of participants in order to establish the effectiveness of PA 109 in relieving the symptoms of benign prostatic hypertrophy.

In addition, a full characterization of what comprises the liposterolic extract of sabal used in the various studies would be necessary in order to describe the ingredient in a drug monograph. Based on the above, the agency concludes that the data and information are insufficient to generally recognize the liposterolic extract of sabal as safe and effective and not misbranded for OTC use as an ingredient in benign prostatic hypertrophy drug products. In addition, there are no well-controlled clinical studies to support general recognition of sabal as safe and effective for this use.

The agency points out that publication of a final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of an application that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to establish a monograph. (See 21 CFR 10.30.)

References

(1) Comment No. LET00001, Docket No. 82N-0168, Dockets Management Branch.

(2) Comment No. CRPT, Docket No. 82N-0168, Dockets Management Branch.

(3) "The Pharmacopoeia of the United States of America," 8th Decennial Rev., United States Pharmacopoeial Convention, J.B. Lippincott Co., Philadelphia, p. 383, 1905.

(4) "The Pharmacopoeia of the United States of America, 9th Decennial Rev.," United States Pharmacopoeial Convention, J.B. Lippincott Co., Philadelphia, pp. 191 and 382, 1916.

(5) "The National Formulary," 5th Ed., American Pharmaceutical Association, The Mack Printing Co., Easton, PA, pp. 45, 46, 96, and 387, 1926.

(6) "The National Formulary 6th Ed.," American Pharmaceutical Association, The Mack Printing Co., Easton, PA, pp. 125, 126, 176, and 317, 1935.

(7) "The National Formulary 7th Ed.," American Pharmaceutical Association, The Mack Printing Co., Easton, PA, pp. 137, 373, and 374, 1942.

(8) "The National Formulary 8th Ed.," American Pharmaceutical Association, The Mack Printing Co., Easton, PA, pp. 457–459, 1946.

(9) Jones, J.M., editor, "Physicians' Desk Reference to Pharmaceutical Specialities and Biologicals," Medical Economics, Inc., Rutherford, NJ, p. 451, 1948.

(10) Cook, E.F., and E.W. Martin, "Remington's Practice of Pharmacy," 10th Ed., The Mack Publishing Co., Easton, PA, pp. 277, 282, and 769, 1951.

(11) "The Homoeopathic Pharmacopoeia of the United States," 8th Ed., The Pharmacopoeia Convention of the American Institute of Homoeopathy, Falls Church, VA, Vol. I, p. 504, 1979.

(12) Sollmann, T., "Irritant Volatile Oils and Related Drugs," *in* "A Manual of Pharmacology and its Applications to Therapeutics and Toxicology," 5th Ed., W. B. Saunders Co., Philadelphia, p. 191, 1936.

(13) Youngken, H.W., "Taxonomic Consideration of Drugs—Drugs of Green Vegetable Origin," *in* "Textbook of Pharmacognosy," 6th Ed., The Blakiston Co., Philadelphia, p. 166–171, 1950.

(14) Champault, G., et al., "Actualite Therapeutique: Traitement Medical De l'Adenome Prostatique," certified translation included, *Annals Urologica*, 6:407–410, 1984.

(15) Griffiths, D.J., and H. Abrams, "The Assessment of Prostatic Obstruction from Urodynamic Measurement and from Residual Urine," *British Journal of Urology*, 51:129–134, 1979.

(16) Hinman, F., and C.E. Cox, "Residual Urine Volume in Normal Male Subjects," *The Journal of Urology*, 97:641–645, 1967.

(17) Tasca, A., et al., "Trattamanto Della Sintomatologia Ostruttiva de Adenoma Prostatico Con Estratto Di Serenoa Repens," certified translation included, *Minerva Urologica e Nefrologica*, 37:87–91, 1985.

(18) Tanagho, E.A., "Neuropathic Bladder Disorders," *in* "General Urology," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 337, 1978.

(19) Whitfield, H.N., and W.F. Hendry, editors, "Textbook of Genito-urinary Surgery," Churchill Livingstone, New York, pp. 412–413, 1985.

II. The Agency's Final Conclusions on OTC Benign Prostatic Hypertrophy Drug Products

The agency has determined that no active ingredient has been found to be generally recognized as safe and effective and not misbranded for use in relieving the symptoms of benign prostatic hypertrophy. Further, the agency has reassessed the position it stated in the tentative final monograph (52 FR 5406 at 5408), and now concludes, as discussed below, that drug products for the relief of symptoms of benign prostatic hypertrophy should not be available OTC.

In the tentative final monograph, the agency proposed Category I labeling for OTC benign prostatic hypertrophy drug products in the event that data were submitted that resulted in the upgrading of any ingredient to monograph status (52 FR 5409). After reviewing and evaluating the available data, the agency placed the amino acids glycine, alanine, and glutamic acid in Category III in that document (52 FR 5408). In

response to the tentative final monograph, no data were received on the amino acids glycine, alanine, and glutamic acid (alone or in combination) to support their reclassification from Category III to Category I.

One manufacturer did submit data on a liposterolic extract of sabal, PA 109. However, as discussed in paragraph I above, none of the studies submitted for PA 109 demonstrated any clinical significance of symptomatic relief of benign prostatic hypertrophy.

At this time, the agency is not aware of any definitive clinical trials with appropriate controls to support effectiveness of these or any other ingredients for OTC use in relieving the symptoms of benign prostatic hypertrophy. The agency finds that surgery is currently the only effective treatment for obstructive benign prostatic hypertrophy. Consequently, after reassessing the potential natural course of the disease condition of benign prostatic hypertrophy, the agency has concluded that OTC benign prostatic hypertrophy drug products labeled for symptomatic relief should not be available. The agency is concerned that "relief of symptoms" alone is not sufficient to ensure the safety and health of individuals with this condition.

Benign prostatic hypertrophy is a condition that causes progressive vesical obstruction to the flow of urine and, in later stages, causes back pressure in the kidneys (hydronephrosis) and contributes to the establishment of infection in the urinary tract (Ref. 1). As prostatic obstruction progresses, about 50 to 80 percent of men will develop unstable bladders with secondary symptoms of frequency, urgency, and urgency incontinence (Ref. 2). Although some of the symptoms (frequency, nocturnal micturition, dysuria) are considered irritative only and may be partially relieved by currently marketed products, other symptoms such as residual urine, which is common in bladder neck obstruction (enlarged prostate), can cause serious complications. Currently, no definitive evidence has been provided to indicate that any drug product offered OTC for the relief of the symptoms of this condition would alter the obstructive or inflammatory signs and symptoms of benign prostatic hypertrophy. For example, although the results of the Champault study discussed above show a statistically significant decrease in the values for residual urine (i.e., 94.7 mL to 55.05 mL), the clinical benefit was not evident because the decrease in residual urine did not result in adequate significant relief of the overall symptom or urine retention. The agency is concerned because chronic urine retention could result in stagnation of urine, which leads to infection. This infection may spread throughout the entire urinary system. Once established, infection is difficult and at times impossible to eradicate even after the obstruction has been relieved. In addition, often the invading organisms are urea-splitting, causing the urine to become alkaline, in which case calcium salts precipitate and form bladder or kidney stones more easily. Secondary infection increases the susceptibility to renal damage (Ref. 3).

In the tentative final monograph, the agency proposed a warning stating, "Because this drug relieves only the symptoms of enlarged prostate without affecting the disease itself, periodic reexamination by a doctor is strongly recommended." (See 52 FR 5406 at 5408.) However, after reevaluating this disease condition, the agency no longer believes that this proposed warning represents adequate labeling. The agency is concerned that, as long as only the symptoms of the condition are relieved, individuals who fear surgery may be lulled into a false sense of security and thus delay reexamination by a physician, resulting in a delay in treatment of the disease. Therefore, the agency believes that providing symptomatic relief without eliminating, arresting, or treating the obstructive causes of benign prostatic hypertrophy will mask the potential of the condition's progression and result in delayed diagnosis of secondary complications, i.e., stagnation of residual urine, urinary tract infection, and potential renal damage.

The agency now concurs with the Panel that benign prostatic hypertrophy drug products are not generally recognized as safe and effective for OTC use and that no ingredient or mixture of ingredients should be available OTC to treat the symptoms of benign prostatic hypertrophy. Therefore, all benign prostatic hypertrophy ingredients, including but not limited to sabal and the amino acids glycine, alanine, and glutamic acid (alone or in combination), which were reviewed by the Panel and the agency, are considered nonmonograph ingredients and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and are new drugs under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

References

(1) Smith, D.R., "Tumors of the Genitourinary Tract," *in* "General Urology," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 284, 1978.

(2) Walsh, P.C., "Benign Prostatic Hyperplasia," *in* "Campbell's Urology," 5th Ed., W.B. Saunders Co., Philadelphia, p. 1259, 1986.

(3) Tanagho, E.A., "Urinary Obstruction and Stasis," *in* "General Urology," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 127, 1978.

The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC benign prostatic hypertrophy drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC benign prostatic hypertrophy drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment

nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in part 310 as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.532 is added to Subpart E to read as follows:

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

(a) The amino acids glycine, alanine, and glutamic acid (alone or in combination) and the ingredient sabal have been present in over-the-counter (OTC) drug products to relieve the symptoms of benign prostatic hypertrophy, e.g., urinary urgency and frequency, excessive urinating at night, and delayed urination. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use in relieving the symptoms of benign prostatic hypertrophy. In addition, there is no definitive evidence that any drug product offered for the relief of the symptoms of benign prostatic hypertrophy would alter the obstructive or inflammatory signs and symptoms of this condition. Therefore, self-medication with OTC drug products might unnecessarily delay diagnosis and treatment of progressive obstruction and secondary infections. Based on evidence currently available, any OTC drug product containing ingredients offered for use in relieving the symptoms of benign prostatic hypertrophy cannot be generally recognized as safe and effective.

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

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use to relieve the symptoms of benign prostatic hypertrophy is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After August 27, 1990, any such OTC 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.

Dated: December 18, 1989.

James S. Benson,

Acting Commissioner of Food and Drugs.

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