

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 369

[Docket No. 95N-0060]

Over-the-Counter Drug Products Containing Phenylpropanolamine; Required Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing new warning labeling for all over-the-counter (OTC) drug products containing phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, and phenylpropanolamine maleate). Phenylpropanolamine is a sympathomimetic drug that is used in OTC weight control, cough-cold, nasal decongestant, and allergy drug products. The warnings will advise consumers not to take more than the recommended dose of phenylpropanolamine, not to take phenylpropanolamine with certain prescription drugs, and not to take phenylpropanolamine under certain conditions. The warnings will also advise consumers that they should not take a phenylpropanolamine drug product with any other drug product containing the ingredients phenylpropanolamine, phenylephrine, pseudoephedrine, or ephedrine, which are sympathomimetic drugs commonly found in allergy, asthma, cough-cold, nasal decongestant, and weight control drug products. These drugs could be harmful if taken together.

DATES: Submit comments on the proposed regulation by May 14, 1996. Written comments on the agency's economic impact determination by May 14, 1996. FDA is proposing that any final rule based on this proposal be effective 6 months after the date of its publication in the Federal Register.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-105), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2304.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of September 9, 1976 (41 FR 38312), the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel) recommended that phenylpropanolamine be classified in Category I (generally recognized as safe and effective, and not misbranded) for nasal decongestant use at adult oral dosages equivalent to the following phenylpropanolamine hydrochloride dosages: 25 milligrams (mg) every 4 hours (h) or 50 mg every 8 h, not to exceed 150 mg in 24 h (41 FR 38312 at 38420). The agency has allowed these dosages for phenylpropanolamine hydrochloride for OTC cough-cold use and is including these dosages in this proposal. The Federal Register of February 26, 1982 (47 FR 8466), the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel) recommended that phenylpropanolamine hydrochloride be classified as Category I for weight control use in adult oral dosages of 25 to 50 mg, not to exceed 150 mg daily. As discussed below, the agency has limited OTC phenylpropanolamine hydrochloride dosages for weight control to 75 mg daily and, based on its indication for use, is including that dosage in this proposal.

After the Miscellaneous Internal Panel completed its report, the agency became aware of studies indicating that certain dosages of phenylpropanolamine cause blood pressure elevation. These studies were discussed in the preamble to the advance notice of proposed rulemaking for OTC weight control drug products (47 FR 8466 through 8468). At that time, the agency specifically requested comments and information on the extent to which phenylpropanolamine induces or aggravates hypertension. The agency also stated that it would not allow any increase in OTC weight control dosages above those currently permitted: An immediate-release dose of up to 37.5 mg and a time-release dose of up to 75 mg phenylpropanolamine, with the total daily dose not to exceed 75 mg in either case.

Many comments were submitted in response to the agency's request for information concerning the safety of phenylpropanolamine. Some comments requested that phenylpropanolamine be removed from the OTC drug market because of its association with increased blood pressure and other adverse effects. Other comments contended that

phenylpropanolamine is safe for OTC use.

After preliminary evaluation of the information submitted by these comments, FDA determined that phenylpropanolamine produces hemodynamic effects (raises blood pressure), but that the data were inadequate to respond to the agency's safety concerns. Subsequently, in meetings with industry on December 2, 1983, and April 11, 1984, the agency discussed its requirements for adequate studies to address this concern about phenylpropanolamine (Refs. 1 and 2). The agency concluded that data were required to: (1) Determine if phenylpropanolamine plays any role in adverse events such as stroke or seizure and other serious adverse reactions that have been reported in association with this drug, and (2) provide information on other possible risk factors (e.g., age, hypertension, concomitant drug use, or disease conditions) associated with phenylpropanolamine use.

In response to the agency's request for data and information, drug manufacturers submitted new dose-response studies designed to investigate the blood pressure effects of phenylpropanolamine. After reviewing all available information, FDA remains concerned about the possibility that phenylpropanolamine used in OTC drug products might increase the risk of hemorrhagic stroke (Ref. 3). The possible risk of stroke is suggested by a relatively small number of spontaneous reports (published and unpublished) of intracranial bleeding, typically in young, female users of phenylpropanolamine weight control drug products, and by the known ability of phenylpropanolamine to transiently increase blood pressure (Ref. 4). A possible mechanism of these reported events, if indeed they are caused by phenylpropanolamine, is an exaggerated hypertensive response, although in most cases no large elevation in blood pressure was detected in association with the hemorrhage. Based on the available data, the agency cannot rule out the possibility that phenylpropanolamine may increase the risk of stroke. This possible risk could be further increased if the recommended dose of phenylpropanolamine was inadvertently exceeded, e.g., taken from two products labeled for different uses.

Because of these concerns, in 1994 the OTC drug industry initiated a large-scale, population-based epidemiologic study of the relationship between OTC phenylpropanolamine drug products and the incidence of hemorrhagic stroke (Ref. 5). However, the study is not expected to be completed until 1998.

The agency believes this study will provide a sufficiently large data base to help determine whether the incidence of stroke associated with ingestion of phenylpropranolamine is greater than the spontaneous rate of stroke, i.e., the rate that would be expected to occur in a similar population not using the drug. The agency does not believe, however, based on information currently available, that phenylpropranolamine used in OTC weight control drug products represents a substantial public health risk. The agency, therefore, does not believe that it is necessary to remove phenylpropranolamine weight control drug products from the OTC market while additional data are being obtained.

While this study is being conducted, the OTC drug industry has proposed additional labeling for OTC phenylpropranolamine weight control drug products to help ensure that their use is confined to adults and that the recommended dose is not exceeded (Ref. 6). Industry's proposal includes a new warning that states: "If nervousness, dizziness, sleeplessness, palpitations, or headache occur, stop using this medication and consult your physician." The proposal also includes a new, separate drug interaction precaution that states:

DRUG INTERACTION PRECAUTION: If you are taking a cough-cold or allergy medication containing any form of phenylpropranolamine, or any type of nasal decongestant, do not take this product. Do not take this product if you are taking any prescription drug, except under the advice and supervision of a physician. Do not use this product if you are presently taking a prescription monoamine oxidase inhibitor (MAOI) for depression or for two weeks after stopping use of an MAOI without first consulting a physician.

In addition, the OTC drug industry's proposal includes a warning that states "Persons between 12 and 18 are advised to consult their physician before using this product." The agency believes that people under 18 years of age should not use an OTC weight control drug product unless specifically directed by a doctor and is modifying that statement in § 201.321(c)(1) of this proposal.

In considering these proposals, the agency notes that the Miscellaneous Internal Panel stated that ingestion of phenylpropranolamine can be expected to cause vasoconstriction, bronchodilation, and tachycardia, because of its alpha and beta adrenergic effects. Large doses would be expected to cause anxiety, excitement, insomnia, headache, cardiac arrhythmias, convulsions, and circulatory collapse (47 FR 8466 at 8474). The Miscellaneous Internal Panel was concerned that a

person might ingest a dose of phenylpropranolamine to reduce nasal congestion and another dose from a different product for weight control, and that the combined doses might have adverse effects. Accordingly, the Miscellaneous Internal Panel recommended a warning statement concerning this possibility on all drug products containing phenylpropranolamine, and included the following language in its monograph for OTC weight control drug products (47 FR 8475): "If you are taking a cough-cold or allergy medication containing any form of phenylpropranolamine, do not take this product."

Many manufacturers of OTC phenylpropranolamine weight control drug products have voluntarily included this warning in product labeling following publication of the Miscellaneous Internal Panel's report. However, the rulemakings for OTC phenylpropranolamine nasal decongestant and weight control drug products will not be completed until after the phenylpropranolamine epidemiologic study is completed and the data assessed. The agency believes that implementation of these warnings should not await the completion of these monograph proceedings, but that a warning should be required on all OTC phenylpropranolamine drug products at this time.

Similarly, because phenylpropranolamine is a sympathomimetic drug (affects the central nervous system, cardiovascular system, and basal metabolic rate), the agency believes that phenylpropranolamine should not be used simultaneously with other sympathomimetic drugs, e.g., pseudoephedrine, ephedrine, or phenylephrine, that would have similar effects on the body. The agency believes that labeling OTC phenylpropranolamine drug products should advise consumers to avoid use while they are using any other sympathomimetic drugs.

FDA concurs with the industry's labeling proposals but has broadened the labeling to include other sympathomimetic drug ingredients and the kinds of products in which they are used. FDA has sufficient concern that adverse reactions could occur from taking phenylpropranolamine in different drug products or from combining sympathomimetic drugs; thus, this information should be included in the "Warnings" statement.

In the final rule for OTC nasal decongestant drug products, published in the Federal Register of August 23, 1994 (59 FR 43386), the agency included a drug interaction precaution

statement regarding the use of sympathomimetic drugs in combination with MAOI drugs. That statement (in § 341.80(c)(1)(i)(D)) (21 CFR 341.80(c)(1)(i)(D)) includes certain conditions (i.e., depression, psychiatric or emotional conditions, Parkinson's disease) for which MAOI drugs are used. A similar statement (but not listing Parkinson's disease) appears in § 341.80(c)(1)(ii)(D) for products labeled for children under 12 years of age. Products labeled for both adults and children under 12 years of age use the statement in paragraph (c)(1)(i)(D). In addition, the statement instructs consumers to consult a health professional if they are uncertain that they are using an MAOI drug. The agency is proposing a shortened version of this precaution statement in the labeling approach used in this current proposal. The agency is asking for comments on how to further shorten or improve this precaution statement. If a shortened version is eventually incorporated in a final rule, the agency will revise § 341.80 accordingly at that time.

II. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Memorandum of meeting between Industry and FDA Personnel, December 2, 1983, coded MM0002, Docket No. 81N-0022, Dockets Management Branch.

(2) Memorandum of meeting between Industry and FDA Personnel, April 11, 1984, coded MM0003, Docket No. 81N-0022, Dockets Management Branch.

(3) Comment No. LET86, Docket No. 81N-0022, Dockets Management Branch.

(4) Blackburn, G.L. et al., "Determinants of the Pressor Effect of Phenylpropranolamine in Healthy Subjects," *Journal of the American Medical Association*, 261:3267-3271, 1989, in Comment No. C94, Vol. 6, Docket No. 81N-0022, Dockets Management Branch.

(5) Comment No. MM11, Docket No. 81N-0022, Dockets Management Branch.

(6) Comment No. C107, Docket No. 81N-0022, Dockets Management Branch.

III. The Agency Proposal

The agency is proposing to amend part 201 (21 CFR part 201) by adding new § 201.321 entitled: "Over-the-counter drugs containing phenylpropranolamine as an active ingredient; required warnings." This section would require new warnings for all OTC drug products containing phenylpropranolamine. The agency has made an effort to shorten and simplify the labeling by combining the warnings and drug interaction precautions under

four new headings in the "Warnings" section. Manufacturers can use bullets or other identifying marks to emphasize the warnings. The format of the "Warnings" section of the product's labeling might look something like the following:

DO NOT TAKE MORE THAN (these words in bold print and capital letters) 75 milligrams per day (24 hours). Taking more can be harmful. **DO NOT TAKE IF** (these words in bold print and capital letters) you have

- Heart or thyroid disease
 - High blood pressure
 - An enlarged prostate gland
- Unless directed by a doctor.

STOP USING IF (these words in bold print and capital letters) you develop

- Nervousness
- Dizziness
 - Sleeplessness
 - Headache
 - Palpitations.

If symptoms continue, ask a doctor. **DO NOT USE WITH** (these words in bold print and capital letters)

- A monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If unsure, ask a health professional.

- Any allergy, asthma, cough-cold, nasal decongestant, or weight control product (containing phenylpropanolamine, phenylephrine, pseudoephedrine, or ephedrine), or any prescription drug, unless directed by a doctor.

The agency is proposing this format as an example of how this warning information might be presented in a clearer and more readable way. The agency is currently considering a new standardized format for the labeling of all OTC drug products. (See the Federal Register of August 16, 1995, 60 FR 42578). Thus, the format proposed in this document may change in the future as a format is developed to label all classes of OTC drug products. At this time, the agency is primarily seeking specific comment on the wording of the proposed warnings for phenylpropanolamine. Comments on the labeling format will also be considered. As discussed below, the agency is encouraging manufacturers to implement this proposed labeling for their phenylpropanolamine drug products as soon as possible. The agency's proposed labeling format or any similar format would be acceptable to use at this time.

The agency is aware that the labeling proposed by the OTC drug industry is currently being used by some manufacturers of OTC phenylpropanolamine weight control drug products. FDA encourages manufacturers of all OTC drug products

containing phenylpropanolamine to implement the agency's proposed labeling statements voluntarily as soon as possible, subject to the possibility that FDA may change the wording of the statements, or not require the statements, as a result of comments filed in response to this proposal. Because FDA is encouraging that the proposed labeling statements be used on a voluntary basis at this time, the agency advises that manufacturers will be given ample time after publication of a final rule based on this proposal to use up any labeling implemented in conformance with this proposal. The agency considers these warnings to be important to the safe use of OTC drug products containing phenylpropanolamine. Therefore, the agency proposes that this new labeling become effective 6 months after the date of publication of the final rule in the Federal Register. The agency proposes to revoke the existing warning statements in § 369.20 (21 CFR 369.20) for "NASAL PREPARATIONS: VASOCONSTRICTORS," and "PHENYLPROPANOLAMINE HYDROCHLORIDE PREPARATIONS, ORAL" at the time that any final rule based on this proposal becomes effective.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule will require some relabeling for products containing phenylpropanolamine. This relabeling will impose direct one-time costs that are expected to be minimal. Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers of drug products containing phenylpropanolamine. Comments regarding the impact of this rulemaking on OTC phenylpropanolamine drug products should be accompanied by appropriate documentation. A period of 90 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed warning statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

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.

VII. Request for Comments

Interested persons may, on or before May 14, 1996, submit written comments on the proposed regulation to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before May 14, 1996. Three copies of all 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 and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201 and 369 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR Part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. New § 201.321 is added to subpart G to read as follows:

§ 201.321 Over-the-counter drugs containing phenylpropranolamine as an active ingredient; required labeling.

(a) Phenylpropranolamine is a sympathomimetic drug used in both over-the-counter (OTC) weight control and nasal decongestant (cough-cold) drug products. The Food and Drug Administration is concerned that adverse reactions could occur if a consumer inadvertently ingests excessive amounts of phenylpropranolamine by taking a weight control and a cough-cold drug product containing phenylpropranolamine concurrently, or by taking products containing phenylpropranolamine and another sympathomimetic drug (nasal decongestant or bronchodilator) concurrently. In addition, because phenylpropranolamine is a sympathomimetic ingredient that interacts with monoamine oxidase inhibitor drugs and can cause serious adverse effects, the two types of drugs should not be taken concurrently. Further, phenylpropranolamine should not be used by persons with high blood pressure, heart or thyroid disease, or diabetes.

(b) Any allergy, cough-cold, or nasal decongestant drug product containing phenylpropranolamine bitartrate, phenylpropranolamine hydrochloride, or phenylpropranolamine maleate as an active ingredient in an oral dosage form for OTC use as described in paragraph (a) of this section is misbranded within

the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) unless its labeling bears the following statements under the heading “WARNINGS:”

(1) *For oral nasal decongestants labeled for adults only or for both adults and children under 12 years of age.*

(i) “DO NOT TAKE MORE THAN” (these five words in bold print and capital letters) (insert maximum 150 mg daily adult dose in a 24-hour period or maximum children’s doses broken down by age groups, expressed in units such as capsules or teaspoonfuls) “per day (24 hours). Taking more can be harmful.”

(ii) “DO NOT TAKE IF” (these four words in bold print and capital letters) “you have heart or thyroid disease, high blood pressure, or an enlarged prostate gland, unless directed by a doctor.” (Information may be indented and/or preceded by a bullet or other identifying mark.)

(iii) “STOP USING IF” (these three words in bold print and capital letters) “you develop nervousness, dizziness, sleeplessness, headache, or palpitations. If symptoms continue, ask a doctor.” (Information may be indented and/or preceded by a bullet or other identifying mark.)

(iv) “DO NOT USE WITH” (these four words in bold print and capital letters) (a) “a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson’s disease), or for 2 weeks after stopping the MAOI drug. If unsure, ask a health professional.” (b) “any allergy, asthma, cough-cold, nasal decongestant, or weight control product (containing phenylpropranolamine, phenylephrine, pseudoephedrine, or ephedrine), or any prescription drug, unless directed by a doctor.” (Statements (a) and (b) under this heading may be indented and/or preceded by a bullet or other identifying mark.)

(2) *For oral nasal decongestants labeled only for children under 12 years of age.* The same labeling of the product contains the same warnings identified in paragraph (b)(i) of this section except that the words “or Parkinson’s disease” under “DO NOT USE WITH” may be deleted.

(c) Any weight control drug product containing phenylpropranolamine bitartrate, phenylpropranolamine hydrochloride, or phenylpropranolamine maleate as an active ingredient in an oral dosage form for OTC use as described in paragraph (a) of this section is misbranded within the meaning of section 502 of the act unless its labeling bears the following

statements under the heading “WARNINGS:”

(1) “For use by people 18 years of age and older.”

(2) “DO NOT TAKE MORE THAN” (these five words in bold print and capital letters) (insert maximum 75 mg daily dose in a 24-hour period, expressed in units such as capsules or tablets) “per day (24 hours). Taking more WILL NOT (these two words in bold print and capital letters) increase weight loss and can be harmful.”

(3) “DO NOT TAKE IF” (these four words in bold print and capital letters) “you have heart or thyroid disease, high blood pressure, or an enlarged prostate gland, unless directed by a doctor.” (Information may be indented and/or preceded by a bullet or other identifying mark.)

(4) “STOP USING IF” (these three words in bold print and capital letters) “you develop nervousness, dizziness, sleeplessness, headache, or palpitations. If symptoms continue, ask a doctor.” (Information may be indented and/or preceded by a bullet or other identifying mark.)

(5) “DO NOT USE WITH” (these four words in bold print and capital letters) (a) “a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson’s disease), or for 2 weeks after stopping the MAOI drug. If unsure, ask a health professional.” (b) “any allergy, asthma, cough-cold, nasal decongestant, or weight control product (containing phenylpropranolamine, phenylephrine, pseudoephedrine, or ephedrine), or any prescription drug, unless directed by a doctor.” (Statements (a) and (b) under this heading may be indented and/or preceded by a bullet or other identifying mark.)

(d) After (date 6 months after date of publication of the final rule in the Federal Register), any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after this date regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

3. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

4. Section 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entries for "NASAL PREPARATIONS: VASOCONSTRICTORS," and "PHENYLPROPANOLAMINE HYDROCHLORIDE PREPARATIONS, ORAL."

Dated: February 6, 1996.

William K. Hubbard,

*Associate Commissioner for Policy
Coordination.*

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