DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 91N-0323]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph for OTC Bronchodilator Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the final monograph for over-the-counter (OTC) bronchodilator drug products to modify the drug interaction precaution statement required in the labeling of OTC bronchodilator drug products containing sympathomimetic amine drugs. These drug products should not be used by persons who are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI), without first consulting a health professional. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: October 20, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION

I. Background

In the Federal Register of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) recommended the following warning statement for the labeling of OTC bronchodilator drug products: "*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor." The warning was based on data showing marked and potentially dangerous increases in blood pressure in patients taking MAOI drugs and sympathomimetic amine bronchodilator drugs (41 FR 38312 at 38370 through 38373).

The agency discussed this statement in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47523, October 26, 1982). In response to the Panel's recommendation, one comment contended that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided (47 FR 47520 at 47523).

The agency acknowledged that the Panel's proposed drug interaction precaution might not be readily understood by all consumers. However, the agency considered a statement of this type to be necessary to alert consumers because antihypertensive and antidepressant drugs are widely prescribed. The agency proposed to simplify the precaution by substituting the term "high blood pressure" for "antihypertensive," and the term "depression" for "antidepressant." The agency also believed that the words "monoamine oxidase inhibitor" would be confusing to consumers and were not needed in the precautionary statement to convey the intended message. Accordingly, the agency proposed the following: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See proposed § 341.76(c)(3) at 47 FR 47527.) In the final monograph for OTC bronchodilator drug products, published in the Federal Register of October 2, 1986 (51 FR 35326 at 35338), the agency substituted the word "use" for the word "take," because "use" can apply to both inhalation and oral dosage forms. This statement appears in § 341.76(c)(4) of the final monograph.

In the Federal Register of June 19, 1992 (57 FR 27662), FDA published a notice of proposed rulemaking to amend the final monograph for OTC bronchodilator drug products to revise the drug interaction precaution to read: "*Drug interaction precaution.* Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product." The agency invited written comments by August 18, 1992, on the specific wording of the warning, and the best way to convey this information to persons who are taking MAOI drugs.

In the Federal Register of August 6, 1992 (57 FR 34733), the agency extended the comment period to October 5, 1992, to obtain additional comments on whether the drug interaction precaution statement should be expanded to include MAO B drugs, such as selegiline. The agency asked whether the proposed drug interaction statement should be expanded to read: "*Drug interaction precaution.* Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product." The agency invited comments and information on interactions between selegiline and sympathomimetic amines and asked whether, from a public health perspective, it would be appropriate to expand the bronchodilator drug interaction precaution, as indicated.

Elsewhere in this issue of the Federal Register, the agency is amending the final monograph for OTC antitussive drug products so that the MAOI drug interaction precautions are consistent for OTC bronchodilator and antitussive products. In a future issue of the Federal Register, the agency intends to include the same drug interaction precautions in the final rule for OTC nasal decongestant drug products. These statements will apply to oral nasal decongestants containing sympathomimetic amine drugs.

In response to the proposed rule, the agency received comments from one physician, one drug manufacturer, and one drug manufacturers' association. Copies of the comments are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. The primary focus of the comments is alternative wording for the new drug interaction precaution statement.

II. The Agency's Conclusions on the Comments

1. One comment stated that the agency's proposal was thorough, contained an excellent review of the existing medical knowledge, and shows

that there is a significant body of information to support the drug interaction precaution. The comment suggested that the drug interaction precautions for OTC antitussive, bronchodilator, and nasal decongestant drug products be consistent because the three groups are quite similar.

The agency agrees that the warning for OTC antitussive, bronchodilator, and oral nasal decongestant drug products should be consistent. Precautions for antitussive and bronchodilator drug products are addressed in this issue of the Federal Register. The same drug interaction precautions will be included in the final monograph for OTC nasal decongestant drug products in a future issue of the Federal Register.

2. One comment was submitted only to the proposed rule for OTC antitussive drug products (Docket No. 90N–0420), but is being discussed here because it pertains to the wording of the drug interaction precaution statement. Based on experience with labeling used on its own dextromethorphan-containing products, the comment suggested the following wording: "*Drug Interaction Precaution:* Do not take this product if you are presently taking a prescription monoamine oxidase inhibitor without first consulting your physician." For products labeled only for children under 12 years of age, the comment suggested: "*Drug Interaction Precaution:* Do not give this product to a child who is presently taking a prescription monoamine oxidase inhibitor without first consulting your child's physician." The comment stated that professional labeling for its dextromethorphan-containing drug products has included an MAOI interaction statement since 1977. The comment added that consumer labeling for its OTC drug product containing dextromethorphan and guaifenesin once used the statement: "*Drug Interaction Precaution:* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression without first consulting your doctor." The same statement was proposed in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47527) and the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220 at 2239, January 15, 1985). The comment complained that this language appeared to cause confusion among health professionals and consumers, so it was subsequently modified to read: "*Drug Interaction Precaution:* Do not take this product if you are presently taking a prescription monoamine oxidase inhibitor without first consulting your physician." The comment stated that this newer language has provided a clear, succinct message to consumers, physicians, and other health professionals. The comment added that when MAOI drugs are prescribed, patients are fully informed about all necessary precautions and are provided with informational brochures on the many foods and drugs with known MAOI interactions.

The agency disagrees that the comment's suggested wording adequately conveys all information necessary for consumers to make an appropriate decision regarding use of the OTC drug product. Specifically, the suggested wording does not include an abbreviated name for monoamine oxidase inhibitor, the likely medical uses for the MAOI, or provide for consultation with health professionals other than doctors. The agency acknowledges that this additional information lengthens the precaution. However, the serious nature of the adverse reactions requires that people taking MAOI drugs should be given as much information as possible, so that they can make the correct decision about the use of the OTC drug product. The term "monoamine oxidase inhibitor" alone is technical and may not be as easily remembered as the shorter term "MAOI." Accordingly, the agency believes that both terms should be used. Some consumers may remember one term, while other consumers may remember the other term. Having both terms in the precaution helps ensure greater recognition among more consumers. Also, those consumers who do not recognize either term may at least recognize that their prescription drug is for one of the indications listed. Hopefully, such persons will consult their doctor or other health professional before taking the OTC drug product. The agency acknowledges that when MAOI drugs are prescribed, patients should be fully informed of the precautions and interactions associated with the drug. However, the agency is concerned that some patients may not be fully informed about the MAOI drug, may not fully understand or remember all the information given them or, with the passage of time, may forget or lose information that has been provided. The agency believes the OTC drug product labeling should be as informative as possible and should reinforce the MAOI prescribing information. Accordingly, the comment's suggested language is not adopted.

3. One comment suggested deleting the statement "If you are uncertain whether your prescription drug contains an MAOI, consult a health professional." The comment stated that a general informational statement urging consumers to use common sense should not be a part of the drug interaction precaution. The comment argued that the statement adds lengthy wording to already crowded labeling, is inappropriately placed as part of a specific warning, is redundant in the contexts of available patient education and of the common sense consumers apply to self-medication practice, and is not supported by adequate documentation or recommendations of the Panel.

The agency disagrees with the comment. The agency included this statement out of concern for consumers who may not understand the technical terms used in the precaution, may not remember whether their prescription drug is an MAOI, or may not retain the informational brochures received when the MAOI drug was prescribed. The agency is also concerned that some consumers who wish to use an OTC drug product may not want to bother their doctor with questions about their medication. Because of the possible severity of the adverse reactions, the agency believes it is important to tell consumers that if there is any uncertainty or doubt about using the OTC drug product, a health professional should be consulted. It is also important to remind consumers who may be reluctant to ask their doctor that other health professionals, such as pharmacists or nurses, can be alternative sources of information. The agency does not believe that label space should limit essential safety information. There are means available to extend label space, such as carton flaps or package inserts. Finally, the wording in this statement is similar to other labeling that the Panel proposed for oral nasal decongestant drug products ("except under the advice and supervision of a physician," 41 FR 38312 at 38423), and to language in the final monograph for OTC bronchodilator drug products ("without first consulting your doctor," § 341.76(c)(4)).

4. One comment urged the agency to include only those aspects of prescription labeling that are formally approved indications. The comment stated that the approved indication for MAOI drugs is depression, and the precaution statement should explicitly reference "depression" and not include overly broad references to unapproved uses, e.g., "emotional disturbances." The comment stated that it is commonplace for prescription drugs, approved for one or more conditions, to be used experimentally in private practice or in formal clinical trials to

treat conditions that do not appear in the approved prescription labeling. The comment asserted, however, that the establishment of OTC drug labeling that would accommodate ever-changing unapproved uses of the prescription drug would abuse the OTC drug product labeling. The comment suggested other approaches, such as notification of physicians and pharmacists by direct mail or through medical publications, press releases, prescription labeling, and professional organizations.

The parenthetical information, "certain drugs for depression or psychiatric or emotional conditions," was intended to alert consumers who may be taking a MAOI drug for a condition other than depression or a condition not readily identified with the term depression, such as anxiety or phobia. The agency noted in the proposal (57 FR 27662) that these uses are described in the scientific literature. In addition, the prescribing information for one MAOI, phenelzine sulfate, states the following: "[Phenelzine sulfate] has been found to be effective in depressed patients clinically characterized as 'atypical,' 'nonendogenous,' or 'neurotic.' These patients often have mixed anxiety and depression and phobic or hypochondriacal features." (Ref. 1). Because people are currently being prescribed MAOI drugs for conditions other than depression, the agency believes that these uses cannot be ignored. Consumers who take the drug for one of these other conditions need to be informed. Further, the language adopted will accommodate a certain amount of increased use of MAOI drugs, as described in the scientific literature, without the need to revise the OTC drug product labeling to cover such uses. The agency does not consider the other approaches suggested by the comment to be adequate because they target the health care professional rather than the consumer. While all of those approaches can and should be used, the consumer must be informed. Therefore, the agency is not adopting the comment's suggestions.

References

(1) Approved labeling for phenelzine sulfate (Parke-Davis), in OTC Vol. 04BFMA2, Docket No. 91N–0323, Dockets Management Branch.

5. One comment suggested that the precaution statement include a 2-week washout period to help ensure that patients will not discontinue the use of the MAOI in order to use the OTC drug. The comment proposed the following wording: "Do not use this product if you are presently taking a prescription monoamine oxidase inhibitor (MAOI) for depression or for 2 weeks after stopping use of a MAOI without first consulting your doctor." The comment stated that the suggested 2-week washout period was based on scientific data, and provided references and studies in support.

One reference provided by the comment stated that the MAOI drugs used clinically in the United States are irreversible enzyme inhibitors, that return of monoamine oxidase activity following administration of an irreversible MAOI is presumably dependent upon enzyme synthesis, and that recovery of monoamine oxidase activity after irreversible inhibition may require up to 2 weeks following withdrawal of the MAOI drug (Ref. 1). Two studies submitted by the comment suggest that the rate of recovery of monoamine oxidase activity may be organ-specific and also possibly influenced by body weight and age (Refs. 2 and 3). In a study with normal volunteers, the apparent half-lives of plasma MAO and platelet MAO were determined to be 2 to 3 days and 9 days, respectively (Ref. 4). In a study of the interaction between sympathomimetic amines (phenylephrine, ephedrine, and noradrenaline) and MAOI's in normal volunteers, results showed a rise in blood pressure from phenylephrine and ephedrine during MAOI administration and for up to 14 days after discontinuation of the MAOI (Ref. 5).

The agency has reviewed the studies and information submitted by the comment and agrees that it is important to include a 2-week washout period in the precaution statement. The prescribing information for MAOI drugs states that 10 to 14 days should elapse between discontinuation of an MAOI and initiation of treatment with certain other drugs, e.g., another antidepressant, another MAOI, or general anesthesia (Refs. 6, 7, and 8). The prescribing information for tranylcypromine sulfate, a partially reversible MAOI, states that monoamine oxidase activity is recovered in 3 to 5 days, and also recommends a 10-day withdrawal period between treatments (Ref. 8).

The agency concludes that information about a withdrawal period is important, for several reasons: (1) It should discourage patients from stopping their MAOI medication to take an OTC cough-cold drug product, and (2) it will help ensure that if the MAOI medication is discontinued for any reason, the OTC drug product will not be used before all or most of the MAOI is no longer in the body. Therefore, the agency is adopting the comment's suggestion to include a 2-week washout period, but is modifying the wording slightly. The comment proposed, "* * * if you are presently taking * * *," which the agency is shortening to "* * * if you are now taking * * *."

References

(1) Baldessarini, R.J., "Drugs and the Treatment of Psychiatric Disorders," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 8th ed., edited by A.G. Gilman et al., Macmillan Publishing Co., New York, pp. 414–419, 1990.

(2) Della Corte; L., and B.A. Callingham, "The Influence of Age and Adrenalectomy on Rat Heart Monoamine Oxidase," *Biochemical Pharmacology*, 26:407–415, 1977.

(3) Planz, G., K. Quiring, and D. Palm, "Rates of Recovery of Irreversibly Inhibited Monoamine Oxidases: A Measure of Enzyme Protein Turnover," *Naunyn-Schmiedeberg's Archives of Pharmacology*, 273:27–42, 1972.

(4) Palm, D. et al., "Quantitation of Irreversible Inhibition of Monoamine Oxidase in Man," *European Journal of Clinical Pharmacology*, 3:82–92, 1971.

(5) Elis, J. et al., "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal*, 2:75–78, 1967.

(6) Approved labeling for phenelzine sulfate (Parke-Davis), in OTC Vol. 04BFMA2, Docket No. 91N–0323, Dockets Management Branch.

(7) Approved labeling for isocarboxazid (Roche), in OTC Vol. 04BFMA2, Docket No. 91N–0323, Dockets Management Branch.

(8) Approved labeling for tranylcypromine sulfate (SmithKline Beecham), in OTC Vol. 04BFMA2, Docket No. 91N–0323, Dockets Management Branch.

6. Two comments discussed possible interactions between MAO B inhibitors, such as selegiline, and OTC drug products containing dextromethorphan or sympathomimetic amines. One comment stated that it had reviewed all spontaneous reports of adverse drug experiences with its MAO B inhibitor drug product containing selegiline, as monitored in accordance with 21 CFR 314.80. The comment found no mention of a suspected drug interaction with, or concomitant use of, an OTC drug product containing dextromethorphan or sympathomimetic amines. The other comment urged the agency to limit drug interaction precautions to those that have been shown to be of significant, practical, and likely importance. Specifically, the comment stated that in the case of the selective MAOI selegiline, the approved indication is Parkinson's disease, but that disease should not be included in the OTC drug product precaution statement because the prescription package insert for selegiline explicitly states that drug-drug interactions are not likely to occur between selegiline and OTC drugs.

The agency disagrees with the comment's interpretation of the package insert for selegiline. The insert (Ref. 1) states the following:

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 milligrams (mg) a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. To date, clinical experience appears to confirm this prediction; cheese reactions have not been reported in selegiline treated patients. The pathophysiology of the "cheese reaction" is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's apparent freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons. However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use.

The insert for selegiline further states:

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed nonselective MAO inhibitors (e.g., tranylcypromine, isocarboxazid, and phenelzine).

The agency is aware that Blackwell has reported that, while selegiline at low dosage inhibits only MAO B, at antidepressant dosages (over 20 mg daily) the drug loses its specificity and hypertensive reactions begin to occur (Ref. 2).

The insert also describes interactions between selegiline and meperidine, which is typical of the interaction of meperidine with other MAOI drugs. The drug interaction section of the insert states: "No interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the data base of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain."

The loss of selectivity at doses higher than 10 mg per day raises concerns that drug interactions may occur. Further, agency does not find the lack of rse reaction reports for selegiline to reassuring. Selegiline is a recently approved new drug with limited marketing experience. In view of the potentially fatal outcome of an interaction between MAOI drugs and sympathomimetic amines and the limited data base for selegiline, the agency believes that the potential for interaction should be assumed and that prudence is the wisest course until more information is available. Therefore, the agency is including the words "Parkinson's disease" in the precaution statement.

References

(1) Approved labeling for selegiline hydrochloride (Somerset), in OTC Vol. 04BFMA2, Docket No. 91N–0323, Dockets Management Branch.

(2) Blackwell, B., "Monoamine Oxidase Inhibitor Interactions with Other Drugs," Journal of Clinical Psychopharmacology, 11:55–59, 1991.

III. The Agency's Final Conclusions on the Drug Interaction Precaution Statement

The agency concludes that a revised drug interaction precaution statement for OTC bronchodilator drug products is needed to better inform consumers of the potential interaction with various MAOI drugs. To be fully informative to consumers, this statement should contain both the technical and abbreviated terms for monoamine oxidase inhibitor (MAOI), should include likely medical uses for the MAOI drugs, should mention a 2-week washout period, and should include the statement to consult a health professional if uncertainty about the MAOI drug exists. Accordingly, the agency is amending § 341.76(c)(4) to read: "*Drug Interaction Precaution.* Do not use this product if you are now taking a prescription 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 you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product."

IV. Economic Impact

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking. 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 bronchodilator 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 bronchodilator drug products is not expected to pose such an impact on small businesses. This final rule imposes one-time costs associated with changing product labels to include the MAOI-bronchodilator interaction precaution statement. In the proposed rule (57 FR 27662 at 27663), the agency encouraged manufacturers of OTC bronchodilator drug products to voluntarily implement this labeling as of the date of publication of the proposal, subject to the possibility that FDA may change the wording of the drug interaction precaution as a result of comments filed in response to the proposal. Because the agency encouraged voluntary implementation of the revised drug interaction precaution statement, manufacturers were advised that they would be given ample time after publication of the final rule to use up any labeling implemented in conformance with the proposal. Any manufacturer that voluntarily implemented labeling in conformance with the proposal and that now needs more than 12 months to use up that labeling should contact the Division of Drug Labeling Compliance (HFD–310), Office of Compliance, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

V. 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.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 341 is amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 341.76 is amended by revising paragraph (c)(4) to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

* * * * *

(c) * * *

(4) "*Drug interaction precaution.* Do not use this product if you are now taking a prescription 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 you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product."

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Dated: August 17, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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BILLING CODE 4160–01–P