

**Brief Summary of OTC Antihistamines with
Chronic Idiopathic Urticaria (CIU) Indication**

I. History of OTC Antihistamines in the U.S.

Schering Corporation has submitted a supplement for loratadine (NDA 19-658) requesting a change of the status from prescription (Rx) to over-the-counter (OTC). Schering Corporation would like to include recurring or chronic hives [chronic idiopathic urticaria (CIU)] in addition to allergic rhinitis as an OTC indication. The Final Rule for OTC antihistamines allows allergic rhinitis as an OTC indication. This document only discusses the history of the Agency's position regarding the OTC use of antihistamines to treat hives.

The Advance Notice of Proposed Rulemaking (ANPR) (41 FR 38312) to establish a monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products was published in September 1976 in combination with recommendations by the Advisory Review Panel (the Panel) on these drug products. The Panel report did not discuss hives as an OTC indication for antihistamines because no data regarding this use was submitted to or reviewed by the Panel. As a result of the ANPR, in January 1985, a Notice of Proposed Rulemaking (NPR) (50 FR 2200) was published. In this notice, one comment requested that hives be included as an indication (Attachment 1); however, no action was taken by the Agency because the comment did not include any data. In addition, hives was not included in the Panel report. Thus, the proposed OTC indications for antihistamines were limited to temporary relief of runny nose, sneezing, itching of nose or throat, and itchy, watery eyes due to hay fever or allergic rhinitis. This NPR also included an indication for temporary relief of runny nose and sneezing associated with the common cold.

The Final Monograph for OTC Antihistamine Drug Products (FM) (57 FR 58356) was published in December 1992. The ingredients listed in this FM are: bromopheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate,

dexchlorpheniramine maleate, diphenhydramine citrate, diphenhydramine hydrochloride, doxylamine succinate, phenindamine tartate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, and triprolidine hydrochloride. In this FM, the Agency addressed two comments recommending “symptomatic treatment of allergic itching” as an indication for antihistamines (Attachment 2). One comment was withdrawn without any explanation. The second comment cited three references demonstrating antihistamine effectiveness in treating manifestations of skin allergies. The comment argued that the data supported an indication for the relief of “itching skin caused by allergy to local irritants such as poison ivy, oak, or sumac, or caused by hives.” The agency disagreed with the comment for the following reasons: (1) hives are a component of systemic anaphylactic reaction and use of antihistamines would delay physician diagnosis and treatment, (2) there was no data demonstrating that the average person can distinguish between a mild allergic reaction and life-threatening condition with similar symptoms, and (3) one reference cited in the comment stated that identification and removal of the cause of urticaria is the ideal treatment. Therefore, the Agency did not support allergic itching as an OTC monograph condition, and the indications listed in the NPR remained unchanged, except for deletion of the “common cold” indication.

II. Foreign Marketing of Loratadine for CIU/Hives

The Agency’s position on the OTC use of antihistamines to treat hives is compared and contrasted to the position taken by foreign health regulatory agencies. Loratadine is available as a prescription drug in 80 countries and as a prescription-free drug in 33 countries (Attachment 3). Prescription-free countries are those that allow loratadine to be purchased from a pharmacist (i.e., “behind-the-counter”) or without the intervention of a pharmacist (i.e., “over-the-counter”).

All 33 prescription-free countries allow allergic rhinitis as an “OTC” indication, but only 29 countries allow hives. One country (Sweden) limits prescription-free loratadine to treatment of allergic rhinitis, but references hives in the indications section of the labeling by stating, “Other areas of application, follow physician’s instructions.” Although hives is an indication on prescription-free loratadine in 29 countries, only 7 countries market this drug “OTC,” while the remaining 22 countries selling these products “behind-the-counter.” The 7 “OTC” countries are: Belgium, Canada, Germany, Ireland, the Netherlands, Russia, and United Kingdom (UK). The Agency is not aware of any foreign health regulatory body retracting loratadine’s prescription-free status.

More information about “OTC” marketing of antihistamines for hives can be gleaned by examining loratadine sales in Canada and UK. Both countries allow allergic rhinitis and hives indications. In Canada, loratadine has been sold “OTC” with these indications since its entry into the market in 1990. Canada’s health regulatory agency allows “OTC” marketing of loratadine as well as many other oral antihistamines. In contrast, UK’s health regulatory body, Medicines Control Agency (MCA), originally classified loratadine with the current indications as Pharmacy (P), meaning it is dispensed by a pharmacist without a prescription. In December 2001, MCA reassigned loratadine to General Sales List (GSL), which corresponds to the U.S. OTC status with a limitation of 7 tablets per package. In the months preceding this reassignment, MCA requested public comment regarding this proposed P-to-GSL switch. MCA received 35 responses with only three objection to the reassignment, and these three responses did not concern hives. The dearth of objections relating to hives may be due to the vast number of P class oral antihistamines having a hives indication. Also, many topical antihistamines with a hives indication are classified as GSL.

The labeling of loratadine products within Canada (Attachment 4) and United Kingdom (Attachment 5) for the treatment or relief of CIU can vary considerably, because the health regulatory agencies in both countries review the labeling of each marketed drug product on an individual basis. Examination of labeling for loratadine products from 18 prescription-free countries, including the 7 "OTC" countries, revealed differing language to describe the CIU indication. Denmark is the only country studied whose labeling referred solely to "urticaria." Labeling from the other 17 countries contained the words such as "hives," "rash," "allergic skin condition," "allergic dermatologic condition," or some combination of these words. Often, one or more of these conditions was combined with "urticaria." Labeling from these countries differed greatly in three areas from the labeling proposed by Schering Corporation (Attachment 6) as follows: (1) Schering Corporation proposed to include the descriptive language "chronic" and "recurring," while "chronic" was only contained on labeling from 12 of the 18 countries, (2) there was not a single foreign label containing the word "idiopathic" or any other language describing the cause of urticaria, (3) none of the foreign labels contained any statement signifying the need for prior physician diagnosis as stated on the proposed U.S. labeling.

List of Attachments

- Attachment 1..... Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Drug Products for Over-the-Counter Human Use; Notice of Proposed Rulemaking
- Attachment 2..... Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Drug Products for Over-the-Counter Human Use; Final Rule
- Attachment 3..... Countries with Prescription-Free Marketing of Loratadine
- Attachment 4..... Loratadine Labeling in Canada
- Attachment 5..... Loratadine Labeling in United Kingdom
- Attachment 6..... Proposed United States Loratadine Labeling by Schering

See hives discussion on next page. Full document follows.

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21 CFR Part 341

Part VIII

Department of
Health and Human
Services

Food and Drug Administration

21 CFR Part 341
Cold, Cough Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-
the-Counter Human Use; Tentative Final
Monograph for OTC Antihistamine Drug
Products

specifically recommended that the warning state "Caution: May cause drowsiness. Alcohol may intensify this effect. Use care when operating a car or dangerous machinery."

The agency agrees with the comments that consumers should be warned that drowsiness is a potential side effect of antihistamine active ingredients. In fact, the Panel recommended the warnings "May cause drowsiness" or "May cause marked drowsiness" in § 341.72(b) (6) and (7) of its monograph. The degree and the frequency of the drowsiness produced by a specific antihistamine active ingredient determines which one of the above warnings is required.

The specific warning suggested by one comment would combine the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or dangerous equipment when taking antihistamines. Combining these related warnings would be beneficial to consumers. However, the agency does not believe that all of the specific language suggested by the comment should be used in the warnings. The comment suggests that the warning "Alcohol may intensify this effect" be substituted for the Panel's recommended warning "Avoid alcoholic beverages while taking this product." The agency has determined that the consumer must be warned to avoid alcohol to ensure the safe use of antihistamines on an OTC basis. Moreover, adding the phrase "alcohol may increase the drowsiness effect" to the warning provides more information to the consumer as to why alcohol should be avoided while taking an antihistamine. The agency has, therefore, included this phrase in the warning.

In addition, the agency believes that revising the Panel's recommended wording " * * * operating heavy machinery" to the wording " * * * operating machinery" better conveys the intent of the Panel. Some equipment that requires mental alertness to operate safely is not "heavy." In addition, warning consumers to use care when operating "dangerous" machinery, as the comment suggests, may not be adequate. Consumers may not consider some machinery dangerous when operated by an alert individual. However, virtually all machinery is potentially dangerous if operated by a person who is drowsy and not alert.

The agency concludes that combining the specific labeling suggested by the comment with the warnings recommended by the Panel, with some modifications, will provide more informative labeling for the consumer. Therefore, the warnings concerning

drowsiness, the use of alcohol, and driving a motor vehicle or operating machinery have been revised in this tentative final monograph. Section 341.72(c)(3) reads as follows: "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery." Section 341.72(c)(4) reads as follows: "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

14. One comment suggested that antihistamines should be labeled to inform consumers that these drugs are useful in treating allergic rhinitis and hives, but should not be labeled for treating the symptoms of asthma.

The Panel recommended that antihistamines be labeled for use in treating symptoms of allergic rhinitis. The agency agrees with the comment and the Panel's recommendations regarding this use.

The Panel recommended as part of § 341.72(b)(2), which has been redesignated § 341.72(c)(2) in the tentative final monograph, that antihistamines be labeled with a warning that persons with asthma should not take them except under the advice and supervision of a physician. The Panel pointed out in its report that many physicians consider the drying side effect of antihistamines to be undesirable in patients with bronchial asthma, and some doctors maintain that such drugs should be contraindicated in patients with this disease. The agency concurs with this recommendation and the warning proposed by the Panel.

Hives as a symptom of an allergic reaction was not included in the Panel's report. No data were submitted to the Panel concerning the use of antihistamines for hives, nor were any data reviewed by the Panel concerning this use of antihistamines. The comment also did not provide any data to substantiate its recommendation. Accordingly, an indication for the use of antihistamines in the treatment of hives as a symptom of an allergic reaction is not being proposed in this tentative final monograph.

15. Several comments pointed out that some OTC products containing antihistamines may be labeled and marketed for use only in pediatric populations. The comments argued that certain warnings and caution statements in the Panel's recommended monograph, i.e., "Do not take this product if you have glaucoma or difficulty in urination due to enlargement of the prostate

gland, avoid driving a motor vehicle or operating heavy machinery, and avoid alcoholic beverages while taking this product," apply only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exemption statement should be added to the monograph under § 341.50(c) stating, "Warnings which are inappropriate for children's products may be eliminated in the labeling of products containing dosage instructions for children only."

The agency agrees that the warnings recommended by the Panel in § 341.72(b)(2), (3), and (4), which have been redesignated as § 341.72(c)(2), (3), and (4) in this tentative final monograph, concerning operating a motor vehicle or machinery, avoiding alcoholic beverages, and the part of the warning statements concerning "difficulty in urination due to enlargement of the prostate gland" are not necessary in the labeling of products intended only for pediatric use. These warnings are not applicable to children and their presence in the labeling would tend to distract parents from label warnings which are important. However, the agency does not agree that the part of the warning about glaucoma in § 341.72(b)(2) should be deleted from the labeling of pediatric products in this tentative final monograph because glaucoma does occur in children (Refs. 1 and 2). In addition, the agency is proposing that the warnings be reworded to reflect the administration of the product by adults rather than self-administration. Accordingly, the tentative final monograph is amended by adding the following to new § 341.72(c):

(6) *For products labeled for children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (g), (h), (i), (j), and (k).* "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride and doxylamine succinate identified in*

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Part VIII

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Cold, Cough Allergy, Bronchodilator, and
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the-Counter Human Use; Tentative Final
Monograph for OTC Antihistamine Drug
Products

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052H]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies, (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with antihistamine drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4950.

SUPPLEMENTARY INFORMATION: In the Federal Register of September 9, 1976 (41 FR 38312) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 12 manufacturers, 2 manufacturers' associations, 16 health care professionals, and 6 health care professional societies submitted comments on antihistamine drug products. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on antihistamine drug products is the fifth segment to be published. The first segment, on anticholinergic drug products and expectorant drug products, was published in the Federal Register of July 9, 1982 (47 FR 30002). The second

segment, on bronchodilator drug products, was published in the Federal Register of October 26, 1982 (47 FR 47526). The third segment, on antitussive drug products, was published in the Federal Register of October 19, 1983 (48 FR 46576). The fourth segment, on nasal decongestant drug products, is being published elsewhere in this issue of the Federal Register. A subsequent segment on combination drug products and general comments will be published in a future issue of the Federal Register.

The advance notice of proposed rulemaking, which was published in the Federal Register on September 9, 1976 (41 FR 38312), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC antihistamine drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC antihistamine drug products.

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the Federal Register of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraph (d); in Subpart B, by adding new § 341.12; and in Subpart C, by adding new § 341.72, and by adding in § 341.90, new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k). This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antihistamine drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979).

(See the Federal Register of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which 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.

Although it was not required to do so under *Cutler*, FDA will no longer use 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 will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug

products (published in the Federal Register of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers, to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can show new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to

the call-for-data notice published in the Federal Register of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products recommended that doxylamine succinate be classified in Category I as an antihistamine at adult oral dosages of 7.5 to 12.5 milligrams (mg) every 4 to 6 hours, not to exceed 75 mg in 24 hours (see 41 FR 38419). However, since the Panel's report was published, controversy has arisen concerning whether or not there is an association of a prescription drug product containing doxylamine succinate with birth defects. This drug product is prescribed as an anti-nauseant for use during pregnancy. In 1982, Eskenazi and Bracken (Ref. 1) reported the results of a case control study of 1747 women, which suggests that a child born to a mother who used the doxylamine containing product was at an approximately four fold increased risk for developing pyloric stenosis. The Boston Collaborative Drug Surveillance Program recently reported to the agency preliminary results of a cohort study that also found an association between exposure to a product containing doxylamine succinate during pregnancy and the occurrence of pyloric stenosis in infants. The reported increase in risk was 2.7 fold, a finding consistent with the Eskenazi and Bracken study. Preliminary results from this study suggest risk increasing with increasing numbers of prescriptions. These reports, however, do not establish that the association is causal. Other factors, in particular, the nausea and vomiting, may account for the observed association. Mitchell et al. (Ref. 2) recently presented the findings of a case-control study conducted by the Drug Epidemiology Unit of Boston University. This study, representing by far the largest available data base, compared the use of a product containing doxylamine succinate among the mothers of 325 infants with pyloric stenosis to its use in mothers of 3,153 infants with other malformations. No association between the use of a product containing doxylamine succinate during pregnancy and the development of pyloric stenosis was found. In addition, the agency has examined Medicaid data to determine whether in this data base there is an association between the use of a doxylamine succinate containing drug

product by women during pregnancy and the occurrence of pyloric stenosis in infants (Ref. 3). Based on an analysis of these data, the agency has concluded that the Medicaid data do not support such an association.

The agency is aware that at this time the scientific and medical communities are actively discussing and debating whether or not doxylamine succinate, in fact, plays a causal role in reported birth defects. This subject has been discussed and debated without resolution at several scientific meetings such as the Teratology Society meeting and the Society for Epidemiologic Research meeting that were held in June 1984. The possible association of doxylamine succinate with birth defects continues to be disputed.

The time necessary to complete a full review and evaluation of the new studies concerning the use of a product containing doxylamine succinate and birth defects could result in a considerable delay in the publication of the tentative final monograph for OTC antihistamine drug products. Accordingly, the agency has decided to remove all discussion of the safety and effectiveness of doxylamine succinate from this document.

The agency intends to review and evaluate the new data and information concerning the relationship between doxylamine succinate and birth defects that is currently being generated in as expeditious a manner as possible. Based on its review and evaluation of the data and information, the agency will publish a separate document in the Federal Register addressing the status of this ingredient.

At this time, drug products containing doxylamine succinate as an OTC antihistamine will remain in the marketplace with the warning required for all OTC drug products, as follows: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

References

- (1) Eskenazi, B., and M. Bracken, "Bendectin (Debenox) as a Risk Factor for Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 144:919-924, 1982.
- (2) Mitchell, A. A., et al., "Birth Defects in Relation to Bendectin Use in Pregnancy II. Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 147:737-742, 1983.
- (3) Rosa, F.W., draft of unpublished study, OTC volume O411TFM, Docket No. 76N-052H, Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Antihistamine Drug Products

1. One comment stated that the Panel gave certain antihistamines (i.e., diphenhydramine, methapyrilene, phenindamine, pheniramine, promethazine, pyrilamine, and thonzylamine) Category I status on the basis of low-quality evidence. The comment stated that the Panel recognized that there were no controlled clinical trials for these drugs, that chronic toxicity studies in animals had not been performed, and that there was no evidence that systematic literature searches were conducted or that FDA adverse reaction files were studied. The comment concluded that these drugs have been adjudged "safe" on the basis of superficial information. The comment contended that controlled clinical trials are required for general recognition of safety and effectiveness. The comment recommended that a complete new review of cough and cold ingredients be conducted by FDA and that FDA impose an immediate ban of all ingredients that are not proven safe and effective by scientific studies equivalent to those required for prescription drugs.

In determining that certain antihistamines should be generally recognized as safe and effective for OTC use, the Panel followed applicable regulations relating to the OTC drug review. The regulations, at 21 CFR 330.10(a)(4)(i), state: "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel's conclusions as to the safety of the aforementioned antihistamine drugs were arrived at in accordance with the above regulation. For the determination of safety, the Panel reviewed published and unpublished studies, Poison Control Center statistics, FDA adverse reaction reports, and other data in the literature, and it used clinical and marketing experience to corroborate these data.

Subsequent to the Panel's determinations, new data were developed concerning some of these ingredients. On the basis of these data, the agency has taken appropriate regulatory action and in this tentative final monograph is making necessary

changes to the Panel's recommendation. For example, the Panel recommended classification of methapyrilene hydrochloride and methapyrilene fumarate in Category I as antihistamines. Subsequent to this recommendation, a National Cancer Institute (NCI) study, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animals and must be considered a potential carcinogen in man. These data are on file in the Dockets Management Branch (address above) under Docket No. 75N-0244 and have been published (Ref. 1).

In June 1979, the agency initiated a recall of all oral and topical products containing methapyrilene. Manufacturers have voluntarily recalled all methapyrilene-containing products from the market, and FDA has withdrawn all NDAs for products containing methapyrilene. Products containing methapyrilene are considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). The agency has therefore placed methapyrilene fumarate and methapyrilene hydrochloride in Category II in this document.

The Panel recommended a Category I classification for promethazine hydrochloride. However, the agency has concerns regarding the safe use of promethazine hydrochloride as an OTC antihistamine and has determined that although promethazine hydrochloride has been widely used as a prescription drug product with a relatively low incidence of serious adverse reactions, at this time general recognition of the safety of this ingredient for long-term use as an OTC antihistamine has not been adequately established. (See comment 9 below.) Therefore, the agency is proposing that promethazine hydrochloride be Category III at this time as an OTC antihistamine.

For the determination of effectiveness, the agency agrees that the studies on which the Panel based its conclusions concerning diphenhydramine hydrochloride, phenindamine tartrate, pyrilamine maleate, and thonzylamine hydrochloride were not well-controlled. However, the Panel reviewed published studies, as cited in its report, and used clinical and marketing experience to corroborate these studies. The agency concludes that the evidence in these studies and the Panel's expertise in evaluating the clinical and marketing experience are sufficient to establish

general recognition of effectiveness of these ingredients as antihistamines.

The agency has reviewed the Panel's recommendations and all of the supporting data and concludes that there is a sufficient basis to determine that brompheniramine maleate, chlorpheniramine maleate, diphenhydramine hydrochloride, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, and thonzylamine hydrochloride are generally recognized as safe and effective when used as ingredients in antihistamine drug products intended for OTC use.

Reference

(1) Lijinsky, W., M. D. Reuber, and B. N. Bläckwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817-819, 1980.

2. Several comments pointed out that the table of symptoms and pharmacological groups in part II, paragraph B. of the Panel's report (41 FR 38320) omitted antihistamines as a pharmacological group for treating runny nose. The comments stated that both the report and the Panel's recommended monograph contain "running nose" as a Category I claim for antihistamines. Several of the comments also criticized the Panel's omission from the table, the report, and the monograph of antihistamines as a pharmacological group for treating "sinus congestion." These comments argued that because "congestion" is a symptom of allergic rhinitis, and the Panel has placed antihistamines in Category I for the alleviation of the symptoms of allergic rhinitis, "sinus congestion" should be included as a symptom to be treated with antihistamines.

The agency agrees the antihistamines were inadvertently omitted from the table of symptoms and pharmacological groups as a treatment for runny nose. Runny nose as may occur in allergic rhinitis is listed as a Category I claim for antihistamines in the Panel's report and in § 341.72(a) (1), (2), and (6) of its recommended monograph. Therefore, the table of symptoms and pharmacological groups in part II, paragraph B. is amended by the publication of this document.

The agency does not agree that antihistamines should be included in the table, report, or recommended monograph for the treatment of "sinus congestion." The Panel recommended antihistamines only for the treatment of specific symptoms, i.e., runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes associated with allergic rhinitis, and did not

recommended antihistamines for the alleviation of all symptoms associated with allergic rhinitis, as stated by the comment. Sinus congestion may result in impaired sinus drainage due to nasal obstruction caused by allergic rhinitis or the "common cold." The Panel reviewed studies that measured the effects of antihistamines or nasal obstructions (Refs. 1, 2, and 3). These studies demonstrated that antihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. To the contrary, the studies indicated that antihistamines may sometimes further aggravate nasal obstruction (Refs. 2 and 3). For that reason, the Panel placed antihistamines in Category 11 for claims for the relief of symptoms such as nasal obstructions, nasal stuffiness, etc. The Comments did not provide any data that demonstrate that antihistamines are effective in the treatment of "sinus congestion." The agency concurs in the Panel's Category II classification.

References

- (1) OTC Volume 040306.
- (2) OTC Volume 040114.
- (3) OTC Volume 040123.

3. One comment stated that two antihistamines should not be taken simultaneously and recommended that the labeling should be clear on this matter. The comment did not further elaborate on its statement.

The comment did not provide any information or examples. It is not clear whether there was concern about the simultaneous ingestion of two drug products each containing antihistamines ingredients that are specifically labeled as "antihistamines" or the simultaneous ingestion of two different drug products both containing antihistamines ingredients but for different use, e.g., one product labeled for "nighttime sleep-aid use" with no labeling as an antihistamine and another product labeled for "antihistamines use."

The agency recognizes that such products are currently available in the OTC drug marketplace but is unaware of any information that would raise health concerns. It is unlikely that a consumer would concurrently take two different OTC drug products both containing antihistamines. The proposed labeling for antihistamines in this tentative final monograph specifically requires that the product's principal intended use, i.e., "antihistamines," be stated in the labeling. By reading the labels, a consumer is made aware that different drug products contain antihistamine intended to treat the same symptoms. Therefore it is unlikely that

two such products would be taken simultaneously.

The agency recognizes that at least one antihistamine ingredient, diphenhydramine hydrochloride, because of its numerous pharmacologic properties, is marketed as an "antihistamines," "antitussive," and "nighttime sleep-aid" drug product. A consumer could simultaneously ingest two such products to alleviate concurrent symptoms. However, the agency is unaware of any information that this does occur. In addition, the agency is unaware of any data demonstrating that the simultaneous ingestion of two antihistamines labeled for different uses would result in a significant safety problem.

Therefore, the agency believes that the proposed labeling for antihistamines drug products in this tentative final monograph is adequate and that at this time there is no justification for expanding the labeling to include specific warnings regarding the simultaneous ingestion of two antihistamines. The agency invites specific comments on this issue.

4. Several comments requested that antihistamines, such as chlorpheniramine maleate, be allowed to make claims for the treatment of symptoms of the common cold. Symptoms for which Category I labeling claims were requested included the relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes when associated with the common cold. Two comments provided new data describing the results of clinical studies in which chlorpheniramine maleate was evaluated for treating symptoms of the common cold (Ref. 1). Another comment stated that there was little evidence to substantiate the usefulness of antihistamines for treating symptoms of the common cold and that, in fact, there are studies that demonstrate a lack of effectiveness for the use of antihistamines in treating symptoms of the common cold. The comment did not identify these studies.

The agency has reviewed the new data submitted in support of the use of chlorpheniramine maleate in treating the symptoms of the common cold enumerated above. The data submitted included independently conducted, multicenter, double-blind studies in which chlorpheniramine maleate was compared with a placebo in patients with the common cold over a 7-day period. In design and overall methodology, these studies follow the guidelines recommended by the Panel for studying antihistamines in the treatment of symptoms associated with

the common cold. An additional study conducted by a single investigator included 196 patients with the common cold who were followed for a 2-day period. This study was similar to the multicentered studies except for the length of time the patients were studied. The studies provide evidence that chlorpheniramine is significantly more effective than a placebo in alleviating the symptoms of runny nose and sneezing associated with the common cold. However, the data do not provide statistical evidence to show that chlorpheniramine is effective in relieving itching of the nose or throat, or itchy, watery eyes associated with the common cold. The agency has, therefore, concluded that chlorpheniramine is effective in treating runny nose and sneezing associated with the common cold. Because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine allow Category I status for these claims to be extended to all Category I antihistamine active ingredients. Accordingly, an indication for the temporary relief of runny nose and sneezing associated with the common cold has been added to proposed § 341.72(b) of this tentative final monograph.

Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

5. One comment recommended that, in view of the reported toxicity of brompheniramine maleate and chlorpheniramine maleate, the quantity of these antihistamines contained in OTC packages should be limited. For example, the comment recommended limiting brompheniramine and chlorpheniramine products to 24 foil-wrapped tablets for the 4-mg strength tablets and to 12 tablets for the 8- and 12-mg strength tablets. The comment also recommended that containers of larger quantities of these antihistamines have child-resistant closures. The comment did not provide any data to support its recommendations.

FDA has established quantity limitations for certain OTC drugs in order to limit the possibility of accidental poisoning of children. See, for example, 21 CFR 201.308 (ipecac syrup) and 21 CFR 201.314 (children's aspirin). The Consumer Product Safety Commission (CPSC), however, has the authority to require child resistant closures for OTC drug containers. FDA is aware that CPSC has reviewed the available data on antihistamines to determine if child-resistant closures are

warranted for OTC drug products containing these ingredients. CPSC has published a final rule that drug products containing more than 75 mg diphenhydramine hydrochloride in a single package and in a dosage form intended for oral administration be required to have child-resistant packaging. (See CPSC Requirements for Child-Resistant Packaging: Diphenhydramine Hydrochloride published in the Federal Register on February 15, 1984; 48 FR 5337.) CPSC found that serious toxic effects can be produced with doses of diphenhydramine hydrochloride as low as 100 mg.

CPSC reviewed the toxicity of antihistamines other than diphenhydramine. However, it did not propose that any antihistamine other than diphenhydramine be required to be packaged with child-resistant closures. Because of the lack of significant toxicity data for antihistamines other than diphenhydramine, CPSC concluded that child-resistant closures were not necessary for these drugs, regardless of the amount of drug contained in each package.

The comment did not submit any data demonstrating a need to limit the package size of non-diphenhydramine antihistamine drug products. Moreover, FDA does not have other data or information showing that limiting the package size for these antihistamines is necessary. In the case of diphenhydramine, CPSC is requiring that child-resistant closures be used for packages of drug products containing greater than 75 mg diphenhydramine. If the agency proposed limiting the package size of such drug products to 75 mg diphenhydramine or less, each package would contain only six children's doses of 12.5 mg or one and one-half adult doses of 50 mg. Limiting the package size to such low numbers of dosages would be impractical. The agency believes that CPSC's requirement for child-resistant closures for drug products containing diphenhydramine provides a sufficient safeguard against accidental overdose in children, and that package size limitations are therefore unnecessary for such drug products.

B. Comments on Switching Prescription Antihistamine Active Ingredients to OTC Status

6. Several comments agreed and others disagreed with the Panel's recommendation to allow the OTC marketing of certain antihistamines which were previously available only by prescription or at higher dosage levels than those currently permitted for OTC

use. The comments which disagreed with the Panel unanimously recommended that those antihistamines which were previously available by prescription only, i.e., promethazine hydrochloride, diphenhydramine hydrochloride, brompheniramine maleate, chlorpheniramine maleate at a dosage of 4 mg, should remain prescription products. In general, the comments expressed opinions, without supporting data, that the benefits obtained from allowing these antihistamines to become available OTC would not outweigh the risks to which consumers would be exposed. Among the risks mentioned were (1) toxic effects from overdosage, (2) varying degrees of drowsiness and different adverse reactions in different patients, (3) a potential for becoming dependent on the sedative effect of antihistamines, (4) the development of a tolerance to antihistamines, and (5) confusion among consumers from too many antihistamines on the market. The comments also expressed concern that asthmatics with severe bronchitis would suffer from a thickening of secretions due to the anticholinergic effect of antihistamines.

In the preamble to the Panel's report at 41 FR 38313, the agency disagreed with the Panel's classification of diphenhydramine hydrochloride as a Category I antihistamine. The agency's objection to the Panel's recommendation to place these ingredients in Category I was based on the degree of drowsiness produced as a side effect. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an OTC antitussive drug product, published in the Federal Register of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." The requirement of child-resistant closures has been addressed in comment 5 above. The agency, therefore, is proposing in this tentative final monograph that diphenhydramine hydrochloride at an adult dosage of 25- to 50 mg and doxylamine succinate at an adult dosage of 7.5 to 12.5 mg every 4 to 6 hours be Category I as OTC antihistamine drug products. (See comments 8 and 15 below.)

The agency disagrees with a comment that contended that higher doses of chlorpheniramine maleate should not be allowed OTC. Chlorpheniramine maleate has been available by prescription at the 4-mg dosage level

and OTC at the 2-mg and the 4-mg dosage levels; however, data reviewed by the Panel shows that chlorpheniramine maleate at a dosage of 4 mg every 4 to 6 hours is the minimum effective dosage for adults. Therefore, the agency is proposing that chlorpheniramine maleate be available OTC at the 4-mg dosage. The warning statements proposed in § 341.72 of this tentative final monograph will advise consumers of the appropriate use of antihistamines and of the risks associated with them. (See comment 12 below.)

The agency agrees with the Panel's classification of brompheniramine maleate and is proposing that this ingredient be Category I.

Issues regarding the safety of promethazine hydrochloride have not yet been resolved. The agency is proposing a Category III classification of this ingredient at this time. (See comment 9 below.)

7. One comment contended that the antihistamine dexchlorpheniramine maleate should be made available OTC. The comment explained that chlorpheniramine maleate, which the Panel classified as a Category I antihistamine, is a mixture of dextro- and levo-optical forms in which most of the activity of the antihistamine results from the dextro-optical form. The comment pointed out that dexchlorpheniramine maleate is composed of the dextro-optical form. The comment argued that a small dose of the more active dexchlorpheniramine would give the same effectiveness as a larger dose of chlorpheniramine and would, therefore, be safer because patients would be exposed to a small amount of active ingredient. The comment cited "The United States Dispensatory" (Ref. 1) in support of its argument, as follows: " * * * it would appear that administration of the dextro isomer in half the dose of the racemic compound would provide practically the same antihistaminic activity as the latter (i.e., chlorpheniramine) and but half of its toxic effects; the expectation has been confirmed clinically." The comment recommended that the agency classify dexchlorpheniramine maleate as a Category I antihistamine in doses of 2, 4, and 6 mg.

Dexchlorpheniramine maleate is currently marketed under an approved abbreviated new drug application (ANDA) as a prescription drug at a dose of 2 mg every 4 to 6 hours for adults, a dose of 1 mg every 4 to 6 hours for children 6 to under 12 years of age, and a dose of 0.5 mg every 4 to 6 hours for children 2 to under 6 years of age (Refs. 2 and 3). Chlorpheniramine maleate is

currently marketed as an OTC antihistamine drug, and the agency is proposing to place chlorpheniramine maleate in Category I at a dose of 4 mg every 4 to 6 hours for adults and a dose of 2 mg every 4 to 6 hours for children 6 to under 12 years of age. (See comment 12 below.)

An in vitro and an in vivo study of dexchlorpheniramine maleate, chlorpheniramine maleate (racemic mixture), and the levo-optical form of chlorpheniramine maleate in guinea pigs and dogs has demonstrated that the dextro-optical form (dexchlorpheniramine maleate) of chlorpheniramine maleate is the active moiety in the racemic mixture (Ref. 4). The data from this study demonstrate that dexchlorpheniramine maleate has approximately twice the antihistaminic activity of chlorpheniramine maleate (racemic mixture). Therefore, the appropriate OTC dosages for dexchlorpheniramine maleate are half the proposed dosages for chlorpheniramine maleate.

A review of FDA adverse reaction reports since 1976 (Ref. 5) indicates that only one adverse reaction (a patient fainting) has been reported in cases where dexchlorpheniramine maleate was the only drug given.

Based on the safe and effective use of dexchlorpheniramine maleate under an approved ANDA, the safe and effective use of chlorpheniramine maleate for many years as an OTC antihistamine, and a review of FDA adverse reaction reports, the agency believes that dexchlorpheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexchlorpheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for chlorpheniramine maleate.

Only timed-release dosage forms are currently approved for adult doses greater than 2 mg every 4 to 6 hours. An approved NDA is required for such products. (See comment 13 below.) Therefore, dosages of 4 to 6 mg will not be included in this tentative final monograph.

Although the agency is proposing in this tentative final monograph to switch

dexchlorpheniramine maleate to OTC use from its present status as a prescription drug, OTC marketing may not begin at this time. In the Federal Register of June 3, 1983 (48 FR 24925), FDA explained the enforcement policy for drugs that were originally on prescription status but which were being proposed for OTC marketing under the OTC drug review. As noted there, 21 CFR 330.13 permits OTC marketing of a drug previously limited to prescription use prior to publication of a final monograph provided that certain conditions are met. To qualify for such treatment, the drug must, at a minimum, have been considered by an OTC drug advisory review panel and either recommended for OTC marketing by the panel or subsequently determined by FDA to be suitable for OTC marketing. Dexchlorpheniramine maleate was not considered by a panel and, therefore, does not qualify for early OTC marketing under the terms of the enforcement policy set out in § 330.13. Moreover, FDA believes that the drug is not appropriate for OTC marketing at this time. FDA believes that public comments submitted in response to the proposed switch in status should be evaluated before OTC marketing is begun. Accordingly, until such comments are reviewed, dexchlorpheniramine maleate remains a prescription drug subject to the terms and conditions specified in its approved ANDA.

References

- (1) Osol, A., R. Pratt, and A.R. Gennaro, "The United States Dispensatory," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 302, 1973.
- (2) Letter from M. Seife, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Copy of FDA-approved labeling from ANDA 86-835, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Roth, F. E., and W. M. Govier, "Comparative Pharmacology of Chlorpheniramine (Chlor-trimeton) and Its Optical Isomers," *Journal of Pharmacology and Experimental Therapeutics*, 124:347-349, 1958.
- (5) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1976-1982, included in OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

8. A number of comments discussed the Panel's recommendation to allow diphenhydramine hydrochloride to be marketed OTC for use as an antihistamine. The comments varied from complete disagreement with the Panel's recommendation to suggestions that the agency place limitations on the

strength of the tablets and/or the size of the packages and that child-resistant closures be required for all OTC products containing this ingredient. One comment suggested that diphenhydramine hydrochloride be available OTC only after consultation with a pharmacist or "prescriber." All of the comments were concerned about diphenhydramine hydrochloride's pronounced tendency for causing drowsiness.

In the preamble to the Panel's report at 41 FR 38313, the agency dissented from the Panel's Category I classification of diphenhydramine hydrochloride as an OTC antihistamine ingredient. It was pointed out that at that time no product containing diphenhydramine hydrochloride was marketed OTC as an antihistamine at any dosage level. In the preamble to the Panel's report, the agency also deferred a decision on the Panel's recommendation to place diphenhydramine hydrochloride in Category I as an antitussive ingredient until the agency made a decision concerning a pending supplemental NDA for OTC status of diphenhydramine hydrochloride as an antitussive. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an antitussive drug product published in the Federal Register of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." Diphenhydramine presently is marketed OTC as an antitussive under an approved supplemental NDA.

The agency believes that the proposed warning in this tentative final monograph that reads, "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery" and the warning for products labeled for children under 12 years of age that reads "May cause marked drowsiness" are adequate to allow OTC marketing of diphenhydramine hydrochloride. These warnings are similar to those required under the approved supplemental NDA for the antitussive drug product containing diphenhydramine.

The agency, therefore, is proposing diphenhydramine hydrochloride as Category I in this tentative final monograph for use as an OTC antihistamine at an adult dosage of 25 to

50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, and for children 6 to 12 years of age at a dosage of 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours.

9. Many comments were opposed to the Panel's classification of promethazine hydrochloride as a Category I antihistamine for relieving the symptoms of allergic rhinitis. These comments agreed with the agency's decision (as stated in the preamble of the Panel's advance notice of proposed rulemaking) to limit promethazine hydrochloride to its present status as a prescription drug. The comments asserted that promethazine should not be available on an OTC basis because of (1) its adverse side effects (especially sedation and blood dyscrasias), (2) the potential for abuse and overdose, (3) the risk in children, and (4) the possibility of increased development of promethazine-induced dyskinesias. The comments concluded that the risk of adverse effects from the OTC availability of promethazine hydrochloride is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Only one comment (a reply comment) agreed with the Panel's Category I classification, contending that promethazine has an outstanding safety record based on its long history of use, that there was no basis for implicating promethazine hydrochloride as the cause for blood dyscrasias, and that promethazine hydrochloride cannot be distinguished from other OTC antihistamines in terms of its sedative and other adverse effects on the central nervous system.

After reviewing these comments, the Center for Drugs and Biologics (CDB) expressed its concerns regarding the effect of promethazine hydrochloride on the central nervous system in a feedback letter to a manufacturer (Ref. 1). Based on an incidence of 1 in 2,468 (0.04 percent) of extrapyramidal syndrome associated with the use of promethazine hydrochloride that was cited by the Panel (41 FR 38390) and a report of four cases of choreoathetosis that were related to the use of promethazine at dosages comparable to those recommended by the Panel (Ref. 2), the CDB questioned whether a drug with the side effect of choreoathetosis and a known incidence of extrapyramidal side effects has an acceptable benefit-to-risk ratio for OTC use. The agency had previously stated in the preamble of the Panel's report (41 FR 38312) that children seem particularly

liable to develop adverse central nervous system reactions, such as extrapyramidal disturbances from the use of promethazine. CDB added that it does not consider the rare drug-related cases of blood dyscrasias an issue that would preclude OTC use of this ingredient inasmuch as other OTC antihistamines also can be associated with such reactions, but because of its other concerns was proposing that promethazine hydrochloride be placed in Category III.

In response to this letter, the manufacturer petitioned the agency to reopen the administrative record for the OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products rulemaking to include new data and information regarding the safety of promethazine hydrochloride (Refs. 3 and 4). The new data and information submitted by the manufacturer clarify the data regarding the incidence of extrapyramidal effects associated with the use of promethazine in both adults and children and point out errors in the data cited by CDB regarding the association between the use of promethazine and the occurrence of choreoathetosis. The agency has included these data and information in the administrative record for this rulemaking in reaching its decision on the status of promethazine in this tentative final monograph (Ref. 5).

The manufacturer noted that the CDB's information on the 0.04 percent incidence rate of extrapyramidal syndrome was based on only one case in 2,468 patients, as cited by the Panel at 41 FR 38390. The manufacturer stated that its review of the single case report disclosed that it involved the injectable dosage form of promethazine and not the oral dosage form. The agency has confirmed that this is correct. The 0.04 percent incidence rate was derived from the Panel's review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program (BCDSP) and the University of Florida Adverse Reaction Study. The manufacturer included in its petition a statement from Jick, a recognized epidemiologist of the BCDSP, that the one case cited by the Panel is the only United States case of extrapyramidal syndrome reported through the BCDSP program (Ref. 4). Jick added that the data in BCDSP were updated through the end of 1981, and four additional cases of extrapyramidal symptoms, all of which were from Western Europe, were identified. Of the four cases, three involved injectable promethazine in relatively high doses, and only one case involved a patient who received oral promethazine. Jick

stated that the patients were elderly, had chronic pulmonary problems and other serious disorders, and received other medications that are likely to have influenced what occurred. Jick concluded that the data do not indicate that promethazine at the suggested OTC oral dosages would present any important risk of the occurrence of extrapyramidal symptoms.

The manufacturer added that the only other reference cited in the agency's letter that describes cases of extrapyramidal effects associated with promethazine was the ADR Highlights (Ref. 2). Fourteen cases are described, of which four purportedly involved promethazine. The manufacturer stated that the ADR Highlights omitted information on the route of administration of the drug in addition to containing other errors on the drugs involved and the doses administered.

The agency acknowledges that inaccuracies existed in the data base and that correction of these errors leads FDA to conclude that the possibility of choreoathetosis occurring with OTC oral doses of promethazine is unlikely. This conclusion is supported by a review of FDA adverse reaction data for the period 1970-1981 and a review of the published literature. These sources reveal only a few cases of extrapyramidal effects possibly associated with dosages of promethazine that would be available OTC. Also, based on the above data, there is no evidence to indicate that these effects would be more likely to occur in children. Based upon the available data, the agency's concerns regarding the occurrence of extrapyramidal effects and choreoathetosis and the concern that children seem particularly liable to develop adverse central nervous system reactions to promethazine have been adequately addressed. Thus, these are no longer issues that would preclude use of this ingredient at proposed OTC oral dosages.

The agency has also reviewed additional information on promethazine obtained from the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI) data systems (Ref. 6). The data show that promethazine hydrochloride has been widely used as a prescription drug product, primarily in combination with other active ingredients, with a relatively low incidence of serious adverse reactions. The agency has further concerns regarding the safe use of this ingredient solely as an OTC antihistamine drug product, particularly for extended periods of time as for

allergy treatment. Promethazine hydrochloride is a phenothiazine, and long-term phenothiazine therapy has been associated with the occurrence of tardive dyskinesia (Ref. 7), a serious central nervous system syndrome that may persist indefinitely after discontinuation of the medication. Some of the comments also expressed concern about the possibility of increased development of promethazine-induced dyskinesias; however, specific cases of the occurrence of tardive dyskinesia with the use of promethazine hydrochloride have not been reported.

Based on data available to the agency (Ref. 6), FDA finds that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis. A review of NPA and NDTI data for the period 1975 to 1981-1982 (Ref. 6) shows that the major use of the manufacturer's promethazine hydrochloride as a prescription drug is in combination products for acute cough/cold therapy. Single entity promethazine hydrochloride tablets are most frequently used for antiemetic actions and have the highest percentage of continued use. The data show that virtually all of the manufacturer's promethazine combination drug products are used for "cough/cold" indications while their use as an "antihistamine/anti-allergy" drug is virtually nil. The data also show that the single-ingredient promethazine drug products (i.e., tablets and syrup) are used as an antihistamine/antiallergy drug to a limited degree (i.e., average of 12 percent of the NDTI mentions for the period 1975 to 1981-1982). In addition, the NDTI data indicate that these promethazine products are used mostly on a short-term rather than on a long-term basis, with the exception of single ingredient tablets (Ref. 6). The high ratios of new to refill prescriptions in the NPA data also demonstrate that these products are not used on a long-term basis with the exception of single ingredient tablets (Ref. 6). Long-term use of the single ingredient tablets most frequently represents its use as an antiemetic in chronic illnesses, such as cancer, and not as an antihistamine in patients with allergic rhinitis. The conclusion that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis is further supported by the manufacturer's statement in its submission that "the average course of therapy under a prescription for an oral promethazine product is about 6-9 days" (Ref. 3).

The agency believes that many consumers who use OTC antihistamines

to treat the symptoms of allergic rhinitis use these products on a long-term basis because the symptoms of allergic rhinitis usually occur for extended periods of time. However, promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis in the OTC target population, i.e., patients with allergic rhinitis. Therefore, there is no assurance that long-term use of promethazine hydrochloride as an OTC antihistamine will not cause the serious side effect tardive dyskinesia.

Accordingly, the agency remains unpersuaded that promethazine, as a phenothiazine, can be generally recognized as safe for OTC use. Many of the comments received in response to the Panel's Category I recommendation for promethazine hydrochloride were from health professionals who opposed OTC status for this drug. The CDB raised the concern in its May 7, 1982 letter that promethazine, as a phenothiazine, is distinct from other antihistamines in terms of its chemical structure and its adverse effects on the central nervous system (Ref. 1). In its petition (Ref. 4), the manufacturer acknowledged that promethazine is chemically related to phenothiazines, but that it is widely recognized that differences in chemical structures and pharmacology substantially lessen the possibility that promethazine could cause the range of side effects associated with other phenothiazines (Ref. 8). The manufacturer also stated that the Panel concluded, after analysis of published reference studies and adverse experience reports on promethazine, that this drug does not cause the wide range of serious or potentially toxic effects that characterize other members of the chemical class of phenothiazines (41 FR 38390). Despite the Panel's recommendation, at this time, FDA is not assured that general recognition of the safety of promethazine hydrochloride for OTC use has been adequately established. The agency is therefore proposing that promethazine hydrochloride as a single ingredient be Category III in this tentative final monograph. The agency specifically invites public comment on the issues discussed above and on the suitability of promethazine hydrochloride for OTC use as a single entity antihistamine drug. Combination drug products containing promethazine hydrochloride will be discussed in the combinations segment of the cough-cold tentative final monograph, in a future issue of the Federal Register.

References

- (1) Letter from W.E. Gilbertson, FDA, to D.L. Shaw, Wyeth Laboratories, coded LET074, Docket No. 76N-052H, Dockets Management Branch.
- (2) Mendelis, P.S., "Antipsychotic Drugs and Chorea/Chorea-like Syndrome," Adverse Drug Reaction Highlights, Division of Drug Experience, Center for Drugs and Biologics, FDA, Rockville, MD, January 25, 1982.
- (3) Comment No. C00168, Docket No. 76N-052H, Dockets Management Branch.
- (4) Comment No. CP0002, Docket No. 76N-052H, Dockets Management Branch.
- (5) Letter from W.F. Randolph, FDA, to S.J. Land and W.W. Vodra, Arnold & Porter, coded PAV, Docket No. 76N-052H, Dockets Management Branch.
- (6) Unpublished data obtained from the National Prescription Audit and the National Disease and Therapeutic Index data systems, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (7) Baldessarini, R.J., "Drugs and the Treatment of Psychiatric Disorders," in "The Pharmacologic Basis of Therapeutics," 6th Ed., edited by A.G. Gilman, L.S. Goodman, and A. Gilman, Macmillan Publishing Co., New York, pp. 391-447, 1980.
- (8) Domino, E.F., "Antipsychotics: phenothiazines, Thioxanthenes, Butyrophenones, and Rowlfia Alkaloids," in "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 471, 1971.

C. Comments on Specific Antihistamine Active Ingredients

10. One comment submitted a study of the effectiveness of phenyltoloxamine citrate to support its reclassification from Category III to Category I as an OTC antihistamine active ingredient (Ref. 1).

The agency has reviewed the study and concludes that this study alone is inadequate to reclassify phenyltoloxamine citrate as a category I antihistamine active ingredient. After a statistical analysis of the data, the agency recognizes that the study demonstrates that there is a statistically significant difference between the pharmacologic action of the placebo and phenyltoloxamine in favor of the active ingredient at 1- and 2-hour intervals after a single dose has been given. However, the study does not demonstrate the effectiveness of phenyltoloxamine over a long enough period of time when given on a dosage schedule that would be representative of the actual conditions under which the drug would be used. The single-dose study can be characterized as a clinical pharmacology study and does not demonstrate that phenyltoloxamine citrate is clinically effective.

Additional data from multiple-dose clinical studies carried out over a period of at least 1 week, and including an adequate number of patients per dose

level as well as placebo, demonstrating the effectiveness of phenyltoloxamine are necessary to reclassify this active ingredient in Category I. There may be a problem of carry-over effect in a crossover study in which each patient is on a drug for a week or more. Therefore, a sufficient washout period should be allowed if a crossover design is used. Phenyltoloxamine citrate will remain in Category III as an OTC antihistamine active ingredient until additional data are received, reviewed, and accepted by the agency.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 2).

References

- (1) Comment Nos. C00168, LET003, and SUP007, Docket No. 76N-0052, Dockets Management Branch
- (2) Letter from W.E. Gilbertson, FDA, to A.D. Flanagan, Warner/Chilcott, coded C00168/ANS, Docket No. 76N-052H, Dockets Management Branch.

D. Comments on Dosages for Antihistamine Active Ingredients

11. Several comments disagreed with the Panel's recommendation to increase the currently available OTC dosage of chlorpheniramine maleate from 2 mg every 4 to 6 hours to 4 mg every 4 to 6 hours with a maximum daily dose of 24 mg. The comments stated that chlorpheniramine maleate has been previously available only by prescription at the 4-mg dosage level and that the increase in dosage from 2 to 4 mg will lead to undesirable side effects, especially excessive drowsiness and overdosage. One comment recommended that chlorpheniramine maleate should continue to be sold OTC in its present dosage form. Another comment stated that the data on which the Panel based its decision to increase the maximum daily dose from 16 to 24 mg were inadequate. The comment explained that the majority of patients treated at the 24-mg daily dosage level were reported in a single uncontrolled study and were selected from a population of patients with a long history of allergy. Many patients had previously received antihistamine therapy. The comment questioned whether this group of patients is appropriate to assess the need for the higher OTC dose of chlorpheniramine maleate. The comment recommended that the maximum daily dose of chlorpheniramine maleate for OTC use be the 16 mg since there are adequate data to support this dosage.

The agency has reviewed these comments and the data evaluated by the Panel and notes the Panel's conclusion

that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg. In addition, chlorpheniramine maleate has been marketed first as a prescription drug product and then as an OTC drug product for many years at the Panel's recommended adult dose of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. The safety and effectiveness of chlorpheniramine maleate at this dosage have been widely recognized. The agency concludes that chlorpheniramine maleate is safe and effective for OTC use at the Panel's recommended 4-mg dosage level. Therefore, it is unnecessary to change the Panel's recommended dosage in this tentative final monograph by restricting the dosage to 16 mg in 24 hours.

13. One comment expressed concern that certain time-release dosage forms containing chlorpheniramine maleate appear to release all of the ingredient in a short period of time. The comment argued that such dumping causes marked drowsiness in some patients. The comment, however, did not make any specific recommendation to the agency.

Timed-release formulations are considered new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). Timed-release formulations are so complex that the state of the art does not permit standardization to the point of inclusion in an OTC drug monograph as a Category I condition. (See 42 FR 56736.) In order to market these drug products, an approved NDA, containing appropriate bioavailability data, is required under section 505 of the act (21 U.S.C. 355) and FDA regulations at Part 314 (21 CFR 314). This requirement is based on the agency's recognition that there is a possibility of overdosage if products that are designed to release the active ingredients over a prolonged period are improperly manufactured, and the active ingredients are released all at once or over too short a time interval.

Chlorpheniramine maleate is generally recognized as safe at an adult oral dosage of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. An NDA is required for any timed-release product containing chlorpheniramine maleate.

E. Comments on Labeling of Antihistamine Drug Product

13. Several comments stressed the importance of making consumers aware through appropriate label warnings that drowsiness is a potential side effect of the use of antihistamines. One comment

specifically recommended that the warning state "Caution: May cause drowsiness. Alcohol may intensify this effect. Use care when operating a car or dangerous machinery."

The agency agrees with the comments that consumers should be warned that drowsiness is a potential side effect of antihistamine active ingredients. In fact, the Panel recommended the warnings "May cause drowsiness" or "May cause marked drowsiness" in § 341.72(b) (6) and (7) of its monograph. The degree and the frequency of the drowsiness produced by a specific antihistamine active ingredient determines which one of the above warnings is required.

The specific warning suggested by one comment would combine the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or dangerous equipment when taking antihistamines. Combining these related warnings would be beneficial to consumers. However, the agency does not believe that all of the specific language suggested by the comment should be used in the warnings. The comment suggests that the warning "Alcohol may intensify this effect" be substituted for the Panel's recommended warning "Avoid alcoholic beverages while taking this product." The agency has determined that the consumer must be warned to avoid alcohol to ensure the safe use of antihistamines on an OTC basis. Moreover, adding the phrase "alcohol may increase the drowsiness effect" to the warning provides more information to the consumer as to why alcohol should be avoided while taking an antihistamine. The agency has, therefore, included this phrase in the warning.

In addition, the agency believes that revising the Panel's recommended wording " * * * operating heavy machinery" to the wording " * * * operating machinery" better conveys the intent of the Panel. Some equipment that requires mental alertness to operate safely is not "heavy." In addition, warning consumers to use care when operating "dangerous" machinery, as the comment suggests, may not be adequate. Consumers may not consider some machinery dangerous when operated by an alert individual. However, virtually all machinery is potentially dangerous if operated by a person who is drowsy and not alert.

The agency concludes that combining the specific labeling suggested by the comment with the warnings recommended by the Panel, with some modifications, will provide more informative labeling for the consumer. Therefore, the warnings concerning

drowsiness, the use of alcohol, and driving a motor vehicle or operating machinery have been revised in this tentative final monograph. Section 341.72(c)(3) reads as follows: "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery." Section 341.72(c)(4) reads as follows: "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

14. One comment suggested that antihistamines should be labeled to inform consumers that these drugs are useful in treating allergic rhinitis and hives, but should not be labeled for treating the symptoms of asthma.

The Panel recommended that antihistamines be labeled for use in treating symptoms of allergic rhinitis. The agency agrees with the comment and the Panel's recommendations regarding this use.

The Panel recommended as part of § 341.72(b)(2), which has been redesignated § 341.72(c)(2) in the tentative final monograph, that antihistamines be labeled with a warning that persons with asthma should not take them except under the advice and supervision of a physician. The Panel pointed out in its report that many physicians consider the drying side effect of antihistamines to be undesirable in patients with bronchial asthma, and some doctors maintain that such drugs should be contraindicated in patients with this disease. The agency concurs with this recommendation and the warning proposed by the Panel.

Hives as a symptom of an allergic reaction was not included in the Panel's report. No data were submitted to the Panel concerning the use of antihistamines for hives, nor were any data reviewed by the Panel concerning this use of antihistamines. The comment also did not provide any data to substantiate its recommendation. Accordingly, an indication for the use of antihistamines in the treatment of hives as a symptom of an allergic reaction is not being proposed in this tentative final monograph.

15. Several comments pointed out that some OTC products containing antihistamines may be labeled and marketed for use only in pediatric populations. The comments argued that certain warnings and caution statements in the Panel's recommended monograph, i.e., "Do not take this product if you have glaucoma or difficulty in urination due to enlargement of the prostate

gland, avoid driving a motor vehicle or operating heavy machinery, and avoid alcoholic beverages while taking this product," apply only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exempting statement should be added to the monograph under § 341.50(c) stating, "Warnings which are inappropriate for children's products may be eliminated in the labeling of products containing dosage instructions for children only."

The agency agrees that the warnings recommended by the Panel in § 341.72(b)(2), (3), and (4), which have been redesignated as § 341.72(c)(2), (3), and (4) in this tentative final monograph, concerning operating a motor vehicle or machinery, avoiding alcoholic beverages, and the part of the warning statements concerning "difficulty in urination due to enlargement of the prostate gland" are not necessary in the labeling of products intended only for pediatric use. These warnings are not applicable to children and their presence in the labeling would tend to distract parents from label warnings which are important. However, the agency does not agree that the part of the warning about glaucoma in § 341.72(b)(2) should be deleted from the labeling of pediatric products in this tentative final monograph because glaucoma does occur in children (Refs. 1 and 2). In addition, the agency is proposing that the warnings be reworded to reflect the administration of the product by adults rather than self-administration. Accordingly, the tentative final monograph is amended by adding the following to new § 341.72(c):

(6) *For products labeled for children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (g), (h), (i), (j), and (k).* "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride and doxylamine succinate identified in*

§ 341.12(e) and (f). "May cause marked drowsiness."

References

- (1) Scheie, H.C., and D.M. Albert, "Textbook of Ophthalmology," 9th Ed., W.B. Saunders Co., Philadelphia, pp. 542-547, 1977.
- (2) Ellis, P.P., and D.L. Smith, "Handbook of Ocular Therapeutics and Pharmacology," 4th Ed., the C.V. Mosby Co., St. Louis, p. 108, 1973.

16. One comment disagreed with the Panel's recommended label warning for pheniramine maleate that states "May cause marked drowsiness." The comment pointed out that pheniramine maleate is in the same chemical class of antihistamines as chlorpheniramine and brompheniramine, i.e., the alkylamines, that this class of antihistamines causes the least amount of drowsiness, and that the Panel recommended the less severe warning "May cause drowsiness" for chlorpheniramine and brompheniramine maleate. The comment urged the agency to require the same label warning, "May cause drowsiness", for pheniramine maleate as allowed for chlorpheniramine and brompheniramine maleate.

The agency has reviewed the data cited in the Panel's report concerning the sedative effects of pheniramine maleate as compared with brompheniramine maleate and chlorpheniramine maleate. In one study reviewed by the Panel, 20 percent of 171 patients receiving a 25-mg dose of pheniramine maleate experienced sedation as a side effect (Ref. 1). In comparison, the Panel states at 41 FR 38382 that brompheniramine maleate produced sedation in 20 percent of less of the individuals taking the ingredient and at 41 FR 38383 that chlorpheniramine maleate produced sedation in 10 to 20 percent of the individuals taking the ingredient. In another study reviewed by the Panel, the frequency of side effects, chiefly drowsiness, seen in 184 subjects receiving 10 mg pheniramine did not exceed the number of side effects in an equal number of subjects receiving a placebo (Ref. 2). Roth and Tabachnick (Ref. 3) have classified the sedative effect of pheniramine maleate as "moderate," compared to a classification of "slight sedation" for brompheniramine maleate and chlorpheniramine maleate. However, Roth and Tabachnick (Ref. 3) did not classify the sedative effect of pheniramine as "marked sedation." The agency agrees with the comment that the warning regarding drowsiness for pheniramine should be the same as that required for chlorpheniramine and brompheniramine. The agency

concludes that the data reviewed by the Panel do not support the need for a stronger warning regarding drowsiness for drug products containing pheniramine maleate. Therefore, the agency proposes to change the warning statement for pheniramine maleate to "May cause drowsiness."

References

- (1) Loveless, M.H., and M. Dworin, "Allergy and Antihistamine Therapy: A Review," *The Bulletin of the New York Academy of Medicine*, 25:473-487, 1949.
- (2) Lowell, F.C., et al., "The Antihistamine Drugs in the Treatment of the Common Cold," *New England Journal of Medicine*, 244:132, 1951.
- (3) Roth, F.E., and I.L.A. Tabachnick, "Histamine and Antihistamine," in "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 1009, 1971.

17. One comment stated that the Panel's recommended warning in § 341.72(b)(8), "Caution: May cause nervousness and insomnia in some individuals," is unnecessary for phenindamine tartrate. The comment cited OTC Volume 040126 (Ref. 1) for review with respect to the necessity for the above warning.

The agency has reviewed six references contained in OTC Volume 040126 that were reviewed and cited by the Panel in its report and finds that insomnia and nervousness are dominant side effects which may occur with the use of phenindamine tartrate. Paul et al. (Ref. 2) evaluated phenindamine tartrate in 260 patients. Sleeplessness occurred in 6.4 percent and nervousness in 5.4 percent. In this study, the total daily dosage ranged from 25 to 150 mg, with most adults taking 25 mg three times a day. McGavack et al. (Ref. 3) found that dryness of the mouth, insomnia, and constipation were the major symptoms in patients receiving a total daily dose of 75 to 600 mg of phenindamine tartrate. Boyd, Weissberg, and McGavack (Ref. 4) found that 24 percent of patients who received a total daily dose of 150 mg experienced insomnia and dryness of the mouth. Crip and Aaron (Ref. 5) evaluated 389 patients who received a dosage of 25 mg of phenindamine tartrate every 4 hours and found that 89 (23 percent) experienced side reactions. Of the 89 patients who had side reactions, 22 percent experienced nervousness and palpitations, 22 percent had nausea, and 10 percent had insomnia.

Pennypacker and Sharpless (Ref. 6) gave patients 25 to 50 mg of phenindamine tartrate daily and found that of 40 patients, 35 percent (14) experienced insomnia and 22.5 percent (9) tenseness. Cohen, Davis, and Mowry

(Ref. 7) studied 292 patients who received a total daily dose of 50 to 200 mg of phenindamine tartrate; 54 of the patients (18 percent) experienced side effects. Of these 54 patients, 33 experienced nervous side reactions.

In other unpublished studies contained in OTC Volume 040126, the recommended effective adult oral dosage of 25 mg of phenindamine tartrate was not used. The evaluations were done with tablets which contained only 10 mg of phenindamine tartrate. For this reason, the data on side effects reported in these studies cannot be used to support the comment's request to eliminate the warning.

Because the data reviewed by the Panel (Refs. 1 through 7) show that phenindamine tartrate may cause insomnia and nervousness, the agency agrees with the Panel's recommendation that the warning, "May cause nervousness and insomnia in some individuals," be required for phenindamine tartrate.

References

- (1) OTC Volume 040126.
- (2) Paul, A.B., et al., "Clinical Evaluation of a New Antihistaminic Compound," *The Laryngoscope*, 58:1044-1054, 1946.
- (3) McGavack, T.H., et al., "Clinical Evaluation of Phenindamine (2-Methyl-9-phenyl-2, 3, 4, 9-Tetra-hydro-1-Pyridindene Hydrogen Tartrate) as an Antihistamine Agent," *American Journal of the Medical Sciences*, 216:437-475, 1948.
- (4) Boyd, L.J., J. Weissberg, and T.H. McGavack, "Tolerance Studies of the Antihistamine Drug Thephorin," *New York State Journal of Medicine*, 49:1596-1598, 1946.
- (5) Crip, L.H., and T.H. Aaron, "Thephorin: An Experimental and Clinical Evaluation in Allergic States," *Journal of Allergy*, 19:303-312, 1948.
- (6) Pennypacker, C.S., and I. Sharpless, "Clinical Study of a New Antihistaminic Drug—Thephorin," *Pennsylvania Medical Journal*, 51:1407-1411, 1948.
- (7) Cohen, E.B., H.P. Davis, and W.A. Mowry, "Thephorin in Allergy," *American Journal of Medicine*, 5:44-47, 1948.

18. One comment stated that the Panel used an inappropriate standard in categorizing some Category II claims and that the claims "fast" and "prompt" were rejected by the Panel for antihistamine labeling because the time is indeterminate. The comment stated that if the drug provides fast or prompt relief, as these terms are understood by consumers, then these claims are not misleading and should be permitted.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients

and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: products statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

As with all OTC drug products, antihistamines are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which antihistamines achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast" or "prompt" are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph.

The agency emphasize that even though terms such as "fast" or "prompt" are outside the scope of the OTC drug review for this class of products, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

Moreover, any statement or term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the Scope of the monograph may be included elsewhere in the labeling, provided the are not false or misleading.

F. Comments on Testing Guidelines

19. Two comments disagreed with the Panel's recommended Category III testing criteria for the evaluation of antihistamines in treating the symptoms of the common cold. (See part VII, paragraph C.2.d. of the Panel's report—Methods of study (41 FR 36396).) The comments argued that it was unreasonable to give the antihistamine throughout the entire course of the cold if the specific symptom being treated, e.g., runny nose, is no longer in

evidence. The comments recommended that the testing criteria be changed so that the study need only be of sufficient length to distinguish clearly between the effect of the drug and the placebo. One of the comments argued that requiring three positive studies from three different investigators, as the Panel recommended, was unnecessary and contended that because two studies were considered adequate in other Category III testing recommended by the Panel, the same requirement should apply in this case.

The other comment argued that the criteria for stratifying patients according to age, sex, and severity of symptoms were unnecessary. The comment contended that stratifying by sex and age would be insignificant as a factor in patients' response to medication and that in view of other strict criteria, which would eliminate potential patients, stratifying by sex and age would result in an additional loss of qualified patients for investigation. The comment believe that stratifying by symptom severity would be too prone to subject interpretation because one could not specify when peak severity would occur in the course of the illness. Both comments recommended that the agency reject the specified panel testing criteria.

The agency has reviewed data in studies designed to demonstrate the effectiveness of the antihistamine chlorpheniramine maleate in treating the symptoms of the common cold that were submitted in response to the advance notice of proposed rulemaking (Ref. 1). Although they do not meet all of the criteria of the Panel's testing guidelines, they have been accepted by the agency as demonstrating the effectiveness of chlorpheniramine for use in treating the symptoms of runny nose and sneezing when associated with the common cold. (See comment 4 above.) One of the acceptable studies did not follow the patients for the entire course of the illness. The study covered the time period over which the symptoms studied were in evidence. Therefore, studies which are of sufficient length to distinguish between the effectiveness of the drug and the placebo in treating a particular symptom are acceptable. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine maleate allow Category I status for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. (See comment 4 above.)

In summary, the agency concludes that adequate data demonstrating the safety and/or effectiveness of a Category III condition are necessary to reclassify that condition to Category I status but that this does not necessarily require that the guidelines recommended by the Panel be followed. The Panel's testing criteria are considered to be recommendations to the agency. Although the submitted chlorpheniramine studies did not stratify patients according to age, sex, severity, and duration of illness, they have been accepted by the agency. Stratification of patients by the above criteria is not a necessary requirement for studies designed to demonstrate the effectiveness of antihistamines in treating symptoms associated with the common cold. Studies submitted in support of the effectiveness and safety of a Category III condition are evaluated on the basis of their own merits rather than on how well they meet the Panel's requirements. However, the agency emphasizes that each study submitted to support a request for the reclassification of a Category III condition to Category I status must substantiate the reclassification whether or not the Panel's recommended guidelines are followed.

Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made some changes in the categorization of antihistamine active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of antihistamine active ingredients recommended by the Panel and the proposed categorization by the agency.

Antihistamine active ingredients	Panel	Agency
Brompheniramine maleate	I	I
Chlorpheniramine maleate	I	I
Doxbrompheniramine maleate	(*)	I
Dexchlorpheniramine maleate	(*)	I
Diphenhydramine hydrochloride	I	I
Methapyrilene fumarate	I	II
Methapyrilene hydrochloride	I	II
Phenindamine tartrate	I	I
Phenindamine tartrate	I	I

Antihistamine active ingredients	Panel	Agency
Phenyltoleramine citrate	III	III
Pitromethazine hydrochloride	I	III
Pyrimamine maleate	I	I
Ternylamine hydrochloride	III	III
Thonzylamine hydrochloride	I	I
Triprolidine hydrochloride	(*)	I

*Not reviewed.

The agency points out that any of the antihistamines proposed as Category I in this tentative final monograph, except dexchlorpheniramine (see comment 7 above), may be marketed OTC in a combination drug product in accord with the Panel's permitted combinations of Category I active ingredients in the analgesic, antitussive, and decongestant categories recommend in § 341.40 of the advance notice of proposed rulemaking (41 FR 38420). The tentative final monograph on cough-cold combination drug products will be published in a future issue of the Federal Register and will discuss the combinations proposed by the agency. Any interim marketing that is permitted is subject to the agency's conclusions in the final monograph.

2. Testing of Category II and Category III conditions. The Panel recommended testing guidelines for antihistamine drug products (41 FR 38329 and 38394). The agency's position regarding the Panel's testing guidelines is discussed in comment 23 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antihistamine ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the antihistamine section of the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency has modified § 341.3(d) and § 341.72(a) (redesignated § 341.72(b) in the tentative final monograph) to include the use of antihistamines for the

temporary relief of runny nose and sneezing associated with the common cold. The agency has reviewed and accepted data which demonstrate the effectiveness of chlorpheniramine maleate in treating these symptoms when associated with the common cold. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted on chlorpheniramine allow an indication for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. The agency proposes to substitute the term "runny" for the term "running" which was used by the Panel. The agency recognizes that the term "runny" is grammatically correct, particularly when it is used in reference to a condition of the nose. The agency believes the term "runny" is more commonly used than the term "running" and is, therefore, better understood by consumers. (See comment 4 above.)

2. Dexbrompheniramine maleate has been marketed as a single ingredient prescription drug product under an approved NDA for 23 years (Ref. 1). It has also been marketed in combination with pseudoephedrine sulfate under an approved NDA for 19 years as a prescription drug product that delivers an adult dose of 2 mg of dexbrompheniramine every 4 hours using a sustained release delivery from a 6-mg tablet taken every 12 hours (Ref. 2). This product has been approved for OTC marketing under an NDA (Ref. 3). The agency has reviewed the literature concerning the safety and effectiveness of dexbrompheniramine maleate as an antihistamine. Based on this literature, and the review by the Drug Efficacy Study Group (DESG) published in the Federal Register of March 19, 1973 (38 FR 7265), the agency believes that the drug can be generally recognized as safe and effective for OTC use.

Dexbrompheniramine maleate is the dextrorotatory isomer (d-isomer) of brompheniramine maleate, which is a racemic histamine antagonist composed of d- and l-isomers. Pharmacological studies have shown that the antihistaminic activity resides almost exclusively in the d-isomer, and that there is very little difference in the toxicities of the d-isomer and the d,l mixture in experimental animals (Ref. 4). Because dexbrompheniramine maleate is about twice as potent as brompheniramine maleate, it is used in clinical practice at one-half the doses of brompheniramine maleate.

The agency has reviewed studies by Frank (Ref. 5), Olansky and Olansky (Ref. 6), and Romanoff and Guidatti (Ref. 7) concerning the safety and effectiveness of dexbrompheniramine maleate alone. The studies showed the drug to be an effective antihistamine, at a dosage of 2 mg, with a low incidence of side effects (drowsiness, slight dizziness). One of the studies, using a double-blind design, showed a significant response to dexbrompheniramine, compared to a placebo, among patients with respiratory symptoms due to allergic rhinitis and pollinosis. Symptoms such as itching, sneezing, and watery eyes were relieved in the patients receiving the drug (Ref. 7).

In addition, the agency has reviewed studies by Mayer and Savitt (Ref. 8), Kapstad and Warland (Ref. 9) Lofkvist and Svenson (Ref. 10), and Fierburg (Ref. 11) concerning the safety and effectiveness of dexbrompheniramine maleate in combination with pseudoephedrine sulfate. All of these studies were double-blinded and evaluated combination drug products that are marketed under the approved NDA (Refs. 8 through 11). The studies were performed in patients with perennial allergic rhinitis or vasomotor rhinitis. A crossover design was used in three of the studies (Refs. 8, 10 and 11). All of these studies demonstrated that dexbrompheniramine maleate in combination with pseudoephedrine sulfate is effective in relieving symptoms when compared to several different reference drugs or placebos. Patients receiving the dexbrompheniramine-pseudoephedrine combination experienced a lessening of sinus congestion and of runny nose. Three other studies, which were not double-blind but controlled clinical comparisons, showed similar results (Refs. 12, 13, and 14).

Side effects reported in these studies were similar to those reported for other antihistamine-nasal decongestant drugs and included drowsiness, dry mouth and dry throat, dizziness, nausea, swelling in the face, headache, restlessness, tachycardia, and constipation. There were relatively few side-effects reported in all, and in only one case did a patient reduce the medication to one tablet a day because of drowsiness and dry mouth (Ref. 5).

A review of FDA adverse reaction reports since 1970 indicates that conditions such as rash, hypertension, transient myopia, nervousness, and insomnia have been reported in cases where the combination drug dexbrompheniramine-pseudoephedrine

was taken (Ref. 15). In these cases, overdose was not indicated, nor was enough information available to indicate a possible cause-and-effect relationship between the use of dexbrompheniramine maleate and the reaction.

Based on the above data and information, the agency believes that dexbrompheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexbrompheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for brompheniramine maleate.

Dexbrompheniramine maleate was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved an NDA that currently allows the OTC marketing of products containing dexbrompheniramine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of dexbrompheniramine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

References

- (1) Letter from I. Siegel, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Letter from J.W. Winkler, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Letter from J.P. Mann, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Roth, F.E., "Antihistamine Activity of the Optical Isomers of Pheniramine and its Chlor- and Brom-Substituted Derivatives," *Chemotherapy*, 3:120-127, 1961.
- (5) Frank, D.L., "Clinical Evaluation of Dexbrompheniramine Maleate (Disomer) in Ear, Nose and Throat Allergies," *Current Therapeutic Research*, 1:115-121, 1959.

(6) Olansky, M., and S. Olansky, "Antihistaminic Activity of Dexbrompheniramine (Disomer). Appraisal in Pediatric Allergies," *Annals of Allergy*, 15:415-419, 1960.

(7) Romanoff, A., and F.P. Guidotti, "Evaluation of Dexbrompheniramine Maleate in Allergy by Double-Blind Procedure. Preliminary Report," *New York State Journal of Medicine*, 60:3800-3803, 1960.

(8) Mayer, P.S., and A.E. Savitt, "Allergic Rhinitis and Air Pollution: A Double-Blind Crossover Analysis," *The Eye, Ear, Nose and Throat Monthly*, 51:9-12, 1972.

(9) Kapstad, B., and A. Warland, "Therapeutic Effectiveness of an Oral Anti-Histamine Combination (Dexbrompheniramine Maleate/D-Isopropylamine Sulfate) in the Treatment of Patients with Allergic Rhinitis," *Acta Allergologica*, 31:233-226, 1976.

(10) Lofkvist, T., and G. Svensson, "A Comparative Evaluation of Oral Decongestants in the Treatment of Vasomotor Rhinitis," *The Journal of International Medical Research*, 6:56-60, 1978.

(11) Fierberg, A.A., "Allergic Nasal Congestion, Effects of Oral Treatment with a Combination of Dexbrompheniramine and D-Isopropylamine," *Annals of Allergy*, 22:324-328, 1964.

(12) Frank, D.L., "Evaluation of Two Sustained-Action Oral Decongestants: A Controlled Study," *Current Therapeutic Research*, 6:158-161, 1964.

(13) Pullen, F.W., and W.W. Montgomery, "Comparative Evaluation of Oral Decongestants," *Archives of Otolaryngology*, 77:10-12, 1963.

(14) Jungert, S., "A Comparison of the Efficacy and Safety of Two Preparations in the Treatment of Allergic and Vasomotor Rhinitis, Disoprol Chronosule Capsules and Tavegil Tablets," *Current Therapeutic Research*, 24:269-273, 1978.

(15) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for 1970-82, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

3. The agency has proposed placing dexchlorpheniramine maleate in Category I based on the safe and effective use of this drug product as a prescription drug under an approved ANDA, a review of FDA adverse reaction reports, and the safe and effective use of the racemic mixture, chlorpheniramine maleate, as an OTC drug product for many years. However, it may not be marketed OTC at this time. (See comment 7 above.)

4. The agency has deleted the reference to methapyrilene in § 341.12(e), the reference to § 341.12(e) in § 341.72(b)(7), and the reference to methapyrilene in § 341.90(f) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for methapyrilene preparations, which are

no longer marketed because of the NCI study showing that these drugs are associated with the development of tumors in laboratory animals. The agency has reclassified methapyrilene preparations in Category II. (See comments 1 and 6 above.)

5. The agency has deleted the reference to promethazine hydrochloride in § 341.12(h), the reference to § 341.12(h) in § 341.72(b)(7), and the reference to promethazine hydrochloride in § 341.90(i) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for promethazine hydrochloride. In the agency's preamble to the Panel's report and recommended monograph (41 FR 38312), the agency disagreed with the Panel's Category I classification of promethazine hydrochloride. The agency concludes that general recognition of the safety of this ingredient for OTC use has not been adequately established. Consequently, the agency has reclassified promethazine hydrochloride in Category III. (See comment 9 above.)

6. Triprolidine hydrochloride has been marketed under an approved NDA for 24 years as a prescription drug product at a dose of 2.5 mg every 6 to 8 hours for adults, a dose of 1.25 mg every 6 to 8 hours for children 6 to 12 years of age, a dose of 0.938 mg every 6 to 8 hours for children 4 to under 6 years of age, a dose of 0.625 mg every 6 to 8 hours for children 2 to under 4 years of age, and a dose of 0.313 mg every 6 to 8 hours for infants 4 months to under 2 years of age (Refs. 1 and 2). In addition, drug products containing triprolidine hydrochloride as a single ingredient and in combination with pseudoephedrine hydrochloride have been approved for OTC marketing under NDAs (Ref. 3). In a 1973 Drug Efficacy Study Implementation (DESI) notice (36 FR 9339), the agency concluded that this drug is effective. FDA has reviewed the literature and marketing history of triprolidine hydrochloride as an antihistamine and believes that this drug can be generally recognized as safe and effective for OTC use.

Studies by Fruchard and Fruchard (Ref. 4); Britton et al. (Ref. 5); Wolfrohm and Liacopoulos (Ref. 6); Bye et al. (Ref. 7); Nicholson (Ref. 8); Bye et al. (Ref. 9); and Peck, Fowle, and Bye (Ref. 10) were reviewed for the safety and effectiveness of triprolidine hydrochloride. Most of the studies were double-blind (Refs. 5, 7, 8, and 9). In 27 out of 36 vasomotor rhinitis cases, triprolidine hydrochloride promptly relieved the symptoms (within 15

minutes), had a long duration of action (about 5 to 6 hours), and was well tolerated (Ref. 6). In another study (Ref. 4), good results were reported in all patients with symptoms of spasmodic rhinitis. These authors also reported that triprolidine hydrochloride acts rapidly and is well tolerated. Both studies (Refs. 4 and 6) indicated that triprolidine is a powerful antihistamine and antianaphylactic agent with mild side effects and rapid action. Studies by Nicholson (Ref. 8) and Peck, Fowle, and Bye (Ref. 10) showed that the effect of triprolidine hydrochloride was immediate and lasts for about 7 hours with a maximum effect at the third hour. The double-blind studies of this drug indicated that, after repeated doses of the drug in a 24-hour period, the degree of drowsiness tended to decrease (Refs. 5, 7, and 9). No evidence of an increased drug effect due to accumulation was reported (Ref. 9). The reported side effects were drowsiness (Refs. 4, 5, 6, 7, and 9) and digestive disturbance (Refs. 4 and 6). FDA adverse reaction reports for triprolidine hydrochloride since 1969 show only two reports of rash (Ref. 11).

Based on the above data and information, the agency is proposing that triprolidine hydrochloride be classified as Category I as an OTC antihistamine at a dose of 2.5 mg every 6 to 8 hours, not to exceed 10 mg in 24 hours, for adults, and a dose of 1.25 mg every 6 to 8 hours, not to exceed 5 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes to place in professional labeling a dose of 0.938 mg every 6 to 8 hours, not to exceed 3.75 mg in 24 hours, for children 4 to under 6 years of age; a dose of 0.625 mg every 6 to 8 hours, not to exceed 2.5 mg in 24 hours, for children 2 to under 4 years of age; and a dose of 0.313 mg every 6 to 8 hours, not to exceed 1.25 mg in 24 hours, for infants 4 months to under 2 years of age. The agency is proposing that the general labeling recommended by the Panel for OTC antihistamine drugs be used for triprolidine hydrochloride.

Triprolidine was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved several NDAs that currently allow the OTC marketing of products containing triprolidine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of triprolidine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and

subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

References

- (1) Letters from P. DeFelice, FDA, to Burroughs-Wellcome Co., Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
 - (2) Copies of FDA-approved labeling from NDA 11-110 and NDA 11-496, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
 - (3) Letters from J.P. Mann, FDA, to Burroughs-Wellcome Co., OTC Volume 04HTFM, Docket No. 76N-052H, Docket Management Branch.
 - (4) Fruchard, J., and J. Fruchard, "Un Nouvel Antihistaminique: Actidil," *Journal de Medecine de Bordeaux et du Sud-Quest*, 134:1356-1358, 1957.
 - (5) Britton, M.G., et al., "Two Doses of Triprolidine for Treatment of Allergic Rhinitis," *Annals of Allergy*, 4(5):330-332, 1979.
 - (6) Wolfrohm, R., and P. Liacopoulos, "Clinical Trial of a New Synthetic Antihistamine-Trans-1 (4 methylephenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-ene Hydrochloride," Extract from *La Semaine des Hopitaux de Paris (La Semaine Medicale Professionnelle et Medico-Sociale)* 13, 1957.
 - (7) Bye, C., et al., "The Effects of Repeated Doses of Triprolidine on Subjective Drowsiness and Performance Tests in Man," *British Journal of Clinical Pharmacology*, 2(4):379p-380p, 1975.
 - (8) Nicholson, A.N., "Effect of the Antihistamines Brompheniramine Maleate and Triprolidine Hydrochloride on Performance in Man," *British Journal of Clinical Pharmacology*, 8:321-324, 1979.
 - (9) Bye, C.E., et al., "Evidence for Tolerance to the Central Nervous Effects of the Histamine Antagonist, Triprolidine, in Man," *European Journal of Clinical Pharmacology*, 12:181-186, 1977.
 - (10) Peck W., A. S. E. Fowle, and C. Bye, "A comparison of triprolidine and Clemastine on Histamine Antagonism and Performance Tests in Man: Implications for the Mechanism of Drug Induced Drowsiness," *European Journal of Clinical Pharmacology*, 8:455-463, 1975.
 - (11) Department of health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969-1982, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
7. The agency has added to § 341.72 a "Statement of identity" paragraph (designated as § 341.72(a)) and a "Directions" paragraph (designated as § 341.72(d)) to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. Inclusion of the "Statement of identity" paragraph has necessitated a redesignation of § 341.72(a) to § 341.72(b), and § 341.72(b) to § 341.72(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the

monograph in Subpart C.

8. The agency has proposed a new indication for the use of antihistamines for the temporary relief of runny nose and sneezing associated with the common cold in paragraph (2) of new § 341.72(b). (See comment 4 and part II, paragraph B. 1, above.) The agency has also combined several required indications under new § 341.72(b)(1). The agency has replaced the Panel's wording "Alleviates, decreases, or temporarily relieves" with the option to select the word "relieves," "alleviates," "decreases," "reduces," or "dries" for the symptom "runny nose" and the option to select the word "relieves," "alleviates," "decreases," or "reduces" for the Symptoms "Sneezing, itching of the nose or throat, and itchy, watery eyes" in the combined indications for antihistamines. These options provide manufacturers the flexibility to select different terms for labeling. Manufacturers are encouraged to submit additional words for possible inclusion as selection options in the "Indications" section of the final monograph for antihistamines drug products. Therefore, indications in § 341.72(a), which has been redesignated § 341.72(b) have been revised as follows: Paragraphs (2), (3), (4), (5), and (6), of § 341.72(a) have been revised and combined in paragraph (1) of new § 341.72(b). The new indication for the use of antihistamines for symptoms associated with the common cold has been added in paragraph (2) of new § 341.72(b). New § 341.72(b) (1) and (2) reflect the combining of indications for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to allergic rhinitis and for the temporary relief of runny nose and sneezing associated with the common cold.

9. The agency has deleted § 341.72(b)(5) of the Panel's recommended monograph. This section provided the warning "Do not give this product to children under 6 years except under advise and supervision of a physician," for all antihistamine drug products. The directions provided under new § 341.72(d) state clearly that a doctor should be consulted for the use of antihistamine drug products in children under 6 years of age. The agency believes that the warning is therefore repetitious and unnecessary.

10. In § 341.72(b) (3), (4), and (8) the Panel recommended the use of the signal word "Caution" in a section of the labeling where the heading "Warnings" is also recommended. The agency notes that historically there has not been a consistent usage for the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and

369.21 (21 CFR 396.20 and 396.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "Caution" has been deleted from this tentative final monograph.

11. The agency has added to § 341.72(b) (redesignated as § 341.72(c)) a paragraph on warnings that are appropriate for products that are labeled for children under 12 years of age. The agency acknowledges that some warnings which the Panel recommended for all antihistamine drug products are inappropriate for products which are labeled for children under 12 years of age. In addition, the warnings for products labeled for children under 12 years of age have been worded to reflect the administration of the product by adults rather than self-administration. (See comment 15 above.)

12. The agency has combined several warnings under new § 341.72(c) and believes that combining the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or machinery while taking antihistamines will provide more informative labeling for the consumer. Therefore, the warnings (in § 341.72(b), which has been redesignated § 341.72(c)), have been revised as follows: Paragraphs (6), (7), and (8) have been redesignated as (3), (4), and (5). Paragraphs (3) and (4) of § 341.72(b) have been revised, combined, and added to paragraphs (3) and (4) of new § 341.72(c). New § 341.72(c) (3) and (4) reflect a combining of warnings concerning drowsiness and the use of alcohol or operating a motor vehicle or machinery while taking antihistamines. (See comment 13 above.)

13. Because antihistamines have an anticholinergic effect which can reduce the volume of bronchial secretions and cause thickening of these secretions, the Panel recommended that antihistamines

bear a warning that people with asthma not take these drugs unless directed by a doctor, and the agency is proposing such a warning in this tentative final monograph. The agency believes that in addition to this warning, the labeling of antihistamine drug products should include a warning against use of antihistamines in patients with any obstructive pulmonary disease in which clearance of secretions is a problem. The Panel stated that it is important to avoid anticholinergics in the presence of bronchial asthma or chronic obstructive pulmonary disease because of the possibility that anticholinergics may cause secretions to become less fluid and difficult to remove, and thus cause obstruction of the respiratory passages (41 FR 38377). The Panel's recommended warning in § 341.72(b)(2) of the advance notice of proposed rulemaking included asthma, but did not include chronic obstructive pulmonary disease as a contraindication for the use of antihistamines. The agency believes that this warning should be expanded to include all types of chronic obstructive pulmonary disease. This term applies to patients with clinically significant, irreversible, generalized airways obstruction associated with varying degrees of chronic bronchitis, abnormalities in small airways, and/or emphysema (Ref. 1). Because respiratory distress symptoms such as difficulty in breathing and shortness of breath are characteristic of chronic obstructive pulmonary disease, the agency believes that such descriptive terms should also be included in the warning in order to provide more information to the consumer. Therefore, the agency is proposing to amend the Panel's recommended warning to read, "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The agency is proposing the term chronic pulmonary disease rather than chronic obstructive pulmonary disease in this warning because it believes that the shorter term will be more understandable to consumers.

Reference

(1) Berkow, R., editor, "The Merck Manual," 14th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, pp. 628-635, 1982.

14. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more

commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing warning and caution statements in §§ 369.20 and 369.21, and exemptions for certain drugs limited by NDAs to prescription sale in § 310.201(a)(13), for oral antihistamine drug products at the time that this monograph becomes effective. The agency proposes to revoke § 310.201(a)(4) and to delete phenyltoloxamine citrate from bearing the warning and caution statements required by § 369.21 at the time that this monograph becomes effective if this ingredient is reclassified in Category I as an OTC antihistamine in the final monograph.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register on 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 proposed rule for OTC antihistamine 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, Public Law 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 antihistamine drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antihistamine drug products. Types of impact may include,

but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC antihistamine drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on antihistamine drug products, a period of 120 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.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, contained in an environmental assessment (under 21 CFR 25.31, proposed in the Federal Register of December 11, 1979; 44 FR 71742), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics, Expectorants, Bronchodilators, Antitussives, Nasal decongestants, Antihistamines.

On July 9, 1982 at 47 FR 40002, FDA proposed to amend 21 CFR Subchapter D by adding a new Part 341. Proposed Part 341, as amended on October 26, 1982 (47 FR 47520) and October 19, 1983 (48 FR 48576) would be further amended as follows:

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed to make the following amendments:

PART 341—[AMENDED]

1. In proposed Subpart A, § 341.3 is amended by adding new paragraph (d) to read as follows:

§ 341.3 Definitions.

(d) *Antihistamine drug*. A drug used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold.

2. In proposed Subpart B, new § 341.12 is added to read as follows:

§ 341.12 Antihistamine active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

- (a) Brompheniramine maleate.
- (b) Chlorpheniramine maleate.
- (c) Dexbrompheniramine maleate.
- (d) Dexchlorpheniramine maleate.
- (e) Diphenhydramine hydrochloride.
- (f) Phenindamine tartrate.
- (g) Pheniramine maleate.
- (h) Pyrilamine maleate.
- (i) Thonzylamine hydrochloride.
- (j) Triprolidine hydrochloride.

3. In proposed Subpart C, new § 341.72 is added and § 341.90 is amended by adding new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k) to read as follows:

§ 341.72 Labeling of antihistamine drug products.

(a) *Statement of identity*. The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antihistamine."

(b) *Indications*. The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to both of the following phrases: (1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "{allergic rhinitis}")."

(2) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing associated with the common cold."

(c) *Warnings*. The labeling of the product contains the following warnings, under the heading "Warnings":

- (1) "May cause excitability especially in children."
- (2) "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of

breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(3) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (f), (g), (h), (i), and (j)*. "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(4) *For products containing diphenhydramine hydrochloride identified in § 341.12(e)*. "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(5) *For products containing phenindamine tartrate identified in § 341.12(f)*. "May cause nervousness and insomnia in some individuals."

(6) *For products that are labeled only for use by children under 12 years of age*. The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (f), (g), (h), (i), and (j)*. "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride identified in § 341.12(e)*. "May cause marked drowsiness."

(d) *Directions*. The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing brompheniramine maleate identified in § 341.12(a)*. Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as

directed by a doctor. Children under 6 years of age: consult a doctor.

(2) For products containing chlorpheniramine maleate identified in § 341.12(b). Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(3) For products containing dexbrompheniramine maleate identified in § 341.12(c). Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) For products containing dexchlorpheniramine maleate identified in § 341.12(c). Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) For products containing diphenhydramine hydrochloride identified in § 341.12(e). Adults: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) For products containing phenindamine tartrate identified in § 341.12(f). Adults: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) For products containing pheniramine maleate identified in § 341.12(g). Adults: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) For products containing pyrillamine maleate identified in § 341.12(h). Adults: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) For products containing thonzylamine hydrochloride identified in § 341.12(i). Adults: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) For products containing tripolidine hydrochloride identified in § 341.12(j). Adults: oral dosage is 2.5 to 6 milligrams every 8 to 8 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 6 to 8 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor. (e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 341.90 Professional labeling.

(b) For products containing bronpheniramine maleate identified in § 341.12(a). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(c) For products containing chlorpheniramine maleate identified in § 341.12(b). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(d) For products containing dexbrompheniramine maleate identified in § 341.12(c). Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(e) For products containing dexchlorpheniramine maleate identified in § 341.12(d). Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(f) For products containing diphenhydramine hydrochloride identified in § 341.12(e). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(g) For products containing phenindamine tartrate identified in § 341.12(f). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(h) For products containing pheniramine maleate identified in § 341.12(g). Children 2 to under 6 years of age: oral dose is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(i) For products containing pyrillamine maleate identified in § 341.12(h). Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 50 milligrams in 24 hours.

(j) For products containing thonzylamine hydrochloride identified in § 341.12(i). Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(k) For products containing tripolidine hydrochloride identified in § 341.12(j). Children 2 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 6 to 8 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 6 to 8 hours, not to exceed 1.252 milligrams in 24 hours.

Interested persons may, on or before May 15, 1985 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests 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. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through

Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data

and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986.

Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-680 Filed 1-14-85; 8:45 am]

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See hives discussion on next 2 pages. Full document follows.

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December 9 1992

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Final Rule

Part IV

**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 201, 310, 341, and 369.
Cold, Cough, Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-
the-Counter Human Use; Final Monograph
for OTC Antihistamine Drug Products;
Final Rule**

consumers to avoid alcoholic beverages when using OTC antihistamines because alcoholic beverages may increase the drowsiness effect of the antihistamine. The agency does not believe that a consumer would equate a drug product containing alcohol with an alcoholic beverage and thus construe these warnings to mean that the drug product should not be used. Additionally, the comment did not provide any data supporting its contention that the proposed warning is confusing. Finally, the agency does not believe that products formulated with alcohol and labeled for nighttime use should have a different warning. The agency is aware that such products often are also labeled for use during the day and are, in fact, used by consumers during the day whether or not they contain labeling for this use. The agency believes that products containing an antihistamine should contain the same warnings, with the only exception being that the word "marked" is required for several of the antihistamines to describe the degree of drowsiness that may occur. Therefore, the agency is not including the comment's suggested alternative in § 341.72(c)(3) and (4) of this final monograph, but is including the warning that was proposed in the amendment to the tentative final monograph for OTC antihistamine drug products, as stated above.

23. One comment suggested that labeling for drug products containing diphenhydramine, chlorpheniramine, and related substances should contain warnings of possible effects on the heart, particularly heart problems requiring treatment with beta blocker drugs. The comment based its suggestion on a personal experience while using a prescription drug product containing diphenhydramine "for a bad case of allergy" and, subsequently, using an OTC drug product containing chlorpheniramine. The comment contended that these drugs "began to cause trouble, a stepped-up heart beat, and a very disabling weak feeling in the chest."

The agency has reviewed the Panel's report with respect to side effects of the antihistamines. The Panel stated that the most common side effects are drowsiness and dryness of the mouth (41 FR 38312 at 38380). The Panel also stated that other side effects which are not as common have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects and cardiovascular symptoms which may include palpitations, hypotension, headache, or tightness of the chest (41

FR 38380). The Panel concluded that serious side effects produced by the antihistaminic drugs in the dosages recommended for OTC use are rare and the more common side effects are rarely serious (41 FR 38380). In addition, in its safety discussions of diphenhydramine (41 FR 38340, 38341, 38384, and 38385), chlorpheniramine (41 FR 38383 and 38384), or any other Category I antihistamine, the Panel did not cite any cardiovascular problems associated with the use of these ingredients as mentioned specifically by the comment. The comment did not submit any data to support its suggestion to add warnings concerning cardiovascular effects to the labeling of OTC antihistamine drug products beyond reporting one personal experience.

Based on the Panel's determination that cardiovascular symptoms rarely occur with the use of OTC antihistamines, and the lack of other information, the agency concludes that there is not an adequate basis for OTC antihistamine drug products to bear label warnings regarding possible adverse cardiovascular effects. Accordingly, the agency is not including such warnings in this final monograph.

24. One comment suggested that all antihistamine drug products contain warnings to the elderly that these products may produce congestion in the lungs, particularly in case of bronchitis, flu, pneumonia, or even a bad cold.

The comment did not provide any data demonstrating that lung congestion results from taking an OTC antihistamine drug product. The agency is not aware of any studies or published literature that would support the comment's statement. If lung congestion occurs when a person has bronchitis, flu, pneumonia, or a bad cold, it would appear that the congestion is likely the result of the underlying condition. The agency does not believe that a warning expanded beyond that discussed in comment 21, "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland," is warranted at this time.

25. Two comments requested that the agency include the symptomatic treatment of allergic itching as a monograph condition in the final monograph for OTC antihistamine drug products. One comment requested this indication specifically for oral diphenhydramine, while the other comment requested the indication for all orally administered OTC antihistamines.

The comment that requested monograph status for oral diphenhydramine requested the following indication: "For temporary relief of itching associated with hives, minor skin irritations, or rashes due to food or animal allergies, insect bites, inhaled allergens (dust, mold, spores), poison ivy, oak, or sumac, soaps, detergents, cosmetics, and jewelry." The comment contended that the proposed indication involves only symptoms which consumers can recognize and treat, and that the indication is currently approved for prescription dispensing of diphenhydramine hydrochloride at the dose already accepted for OTC marketing. This comment was subsequently withdrawn, but no reasons were given (Ref. 1).

The second comment cited statements from three references to support the effectiveness of orally administered antihistamines for the relief of pruritus, angioedema, and other manifestations of skin allergies: (1) prior administration of chlorpheniramine raised the itch thresholds to both 2-methyl histamine and histamine itself (Ref. 2), (2) traditional antihistamines of the H1 type are the mainstay in the management of urticaria (Ref. 3), and (3) certain of the allergic dermatoses respond favorably to H1 blockers; H1 blockers also have a place in the treatment of itching pruritides; and some relief may be obtained in many patients suffering atopic dermatitis and contact dermatitis, although topical corticosteroids seem to be more valuable in such diverse conditions as insect bites and ivy poisonings (Ref. 4). The comment requested that the indications in § 341.72(b) be expanded to permit the following claim: " * * * or the itching skin caused by allergy to local irritants such as poison ivy, oak, or sumac, or caused by hives."

The agency has reviewed the information provided by the comment and determined that it is insufficient to support general recognition of the symptomatic treatment of allergic itching as an appropriate OTC indication for oral antihistamine drug products. Hives and pruritic rashes secondary to foods, animal allergies, and insect stings and bites can be one component of a systemic anaphylactic reaction, and the use of an OTC antihistamine could potentially delay more appropriate treatment that may be needed. The agency is unaware of any data demonstrating that the average person can distinguish between a mild allergic reaction and a life-threatening reaction that may begin with itching only. Histamine is only one of the mediators released during mast cell

degranulation (Ref. 5). Therefore, the use of an antihistamine alone may not be sufficient.

The agency does not find that the references cited by the comment support OTC use of oral antihistamines for pruritus, angioedema, and other manifestations of skin allergies. For example, Monroe (Ref. 3) also said that the ideal treatment for urticaria is identification and removal of its cause and that oral antihistamines of the H1 type are the usual medical treatment for acute urticaria, but medical management is required in severe urticarial reactions. Further, the edition of Goodman and Gilman cited by the comment included in its discussion of allergic dermatoses the caveat that, although angioedema is responsive to treatment with antihistamines, the paramount importance of epinephrine in the severe attack must be emphasized (Ref. 4). This caution is carried through to the current edition of Goodman and Gilman as well (Ref. 5). Poison ivy, oak, and sumac are examples of contact dermatitis. The Merck Manual (Ref. 6) states that, although an oral corticosteroid should be given in severe cases and the treatment for contact dermatitis is usually topical corticosteroids, antihistamines are ineffective in cases of contact dermatitis except for their sedative effect.

Based upon currently available data, the agency concludes that there is a lack of information to support an OTC indication for allergic itching related to hives and rashes. Thus, the use of OTC oral antihistamines for self-treatment of these problems remains a nonmonograph condition at this time.

References

(1) Comment No. WDL 1, Docket No. 76N-052H, Dockets Management Branch.
 (2) Davies, M. G., and M. W. Greaves, "The Current Status of Histamine Receptors in Human Skin: Therapeutic Implications," *British Journal of Dermatology*, 104:601-606, 1981.
 (3) Monroe, E. W., "Treatment of Urticaria," *Dermatologic Clinics*, 3:51-55, 1985.
 (4) Douglas, W. W., "Histamine and 5-Hydroxytryptamine (Serotonin) and Their Antagonists," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 6th Ed., edited by A. G. Gilman, L. S. Goodman, and A. Gilman, Macmillan Publishing Co., New York, pp 622-646, 1980.
 (5) Garrison, J. C., and T. W. Rall, "Histamine, Bradykinin, 5-Hydroxytryptamine, and Their Antagonists," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 8th Ed., edited by A. G. Gilman, et al., Pergamon Press, New York, pp. 574-588.
 (6) Berkow, R., editor, "The Merck Manual," 15th Ed., Merck & Co., Inc., Rahway, NJ, pp. 2255-2257, 1987.

II. Summary of Significant Changes From the Proposed Rule

1. The agency has determined that diphenhydramine citrate should be included in this final monograph because the citrate salt of diphenhydramine is identical to the hydrochloride salt. A dose of 76 mg diphenhydramine citrate supplies an equivalent amount of diphenhydramine content as 50 mg diphenhydramine hydrochloride. Therefore, the agency is revising the letter designations of active ingredients in § 341.12 *Antihistamine active ingredients* to include the addition of diphenhydramine citrate in this section. The agency is also revising and redesignating the paragraphs in §§ 341.72 (c) and (d) and 341.90 to reflect this addition to § 341.12. (See comment 4.)

2. In order to allow for greater flexibility in indication statements, the agency is revising and expanding § 341.72(b) to allow for the option of using either the phrase "Temporarily relieves" or "For the temporary relief of." This revision results in the addition of a new indication in § 341.72(b)(2); proposed § 341.72(b)(2) (indication for a cold) is temporarily removed while the agency further assesses the use of antihistamines for relieving symptoms of a cold. New § 341.72(b)(2) now reads as follows: "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)"). (See comment 14.)

3. The agency is clarifying and revising the warning in § 341.72(c)(2) so that the consumer will not confuse "breathing problems" associated with nasal congestion with "breathing problems" associated with emphysema or chronic bronchitis (conditions for which an antihistamine should not be used) when taking an OTC cough-cold combination drug product containing an antihistamine and a nasal decongestant and to delete the term "asthma." The agency is revising the warning to read as follows: "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland." Likewise, the corresponding warning in § 341.72(c)(6)(i) for products that are labeled only for use by children under 12 years of age is also revised to read as follows: "Do not give this product to children who have a breathing problem such as chronic bronchitis or who have

glaucoma, without first consulting the child's doctor." (See comment 21.)

4. The agency is deferring its final decision on the monograph status of doxylamine succinate. Thus, the agency has deleted this ingredient from § 341.12 of the monograph, all references to this ingredient from headings in the monograph, and the directions for the use of this ingredient from § 341.72(d) and 341.90.

5. The agency is revising the letter designations proposed on January 15, 1985, and August 24, 1987, in the following sections: in § 341.3 *Definitions*, (d) is being redesignated as (e); and in § 341.90 *Professional Labeling*, paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), and (m) have been redesignated as paragraphs (e), (f), (g), (h), (i), (k), (l), (m), (n), (o), (p), and (q), respectively. The redesignated paragraph "l" is being reserved because the agency is deferring its final decision on the status of doxylamine succinate. Also, new paragraph (j) for the ingredient diphenhydramine citrate is being added to § 341.90.

6. The agency is deferring its final decision on the OTC claim for the common cold proposed in § 341.72(b) of the tentative final monograph until the scientific debate about such use is resolved as discussed above. Thus, the agency is deleting the portion of the definition proposed in § 341.3(e) that refers to the common cold and the indication proposed in § 341.72(b) for the use of OTC antihistamines for symptoms of the common cold.

III. The Agency's Final Conclusions on OTC Antihistamine Drug Products for Relief of Symptoms of Hay Fever and Upper Respiratory Allergies (Allergic Rhinitis)

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antihistamine drug products are generally recognized as safe and effective and not misbranded for relief of symptoms of hay fever and upper respiratory allergies (allergic rhinitis). Specifically, the following ingredients are included in this final monograph for OTC antihistamine use: brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, diphenhydramine citrate, diphenhydramine hydrochloride, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, and triprolidine hydrochloride. The following ingredients for OTC

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Final Rule
Department of Health and Human Services
Food and Drug Administration

Part IV

**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 201, 310, 341, and 369
Cold, Cough, Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-
the-Counter Human Use; Final Monograph
for OTC Antihistamine Drug Products;
Final Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 310, 341, and 369

[Docket No. 76N-052H]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antialsthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antihistamine Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis)) are generally recognized as safe and effective and not misbranded. 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 antihistamine drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC antihistamine ingredients that have been found to be not generally recognized as safe and effective or are misbranded and were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: December 9, 1993.

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: In the Federal Register of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel), which was the advisory review panel responsible for evaluating

data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

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. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of tentative final monographs for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, was issued in the following segments: anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The fifth segment, the tentative final monograph for OTC antihistamine drug products, was published in the Federal Register of January 15, 1985 (50 FR 2200). Interested persons were invited to file by May 15, 1985, 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 May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986.

In this tentative final monograph, the agency acknowledged a need to evaluate new data and information concerning doxylamine succinate and birth defects (50 FR 2200 at 2202). This information arose after the Cough-Cold Panel recommended that doxylamine succinate be generally recognized as safe and effective as an OTC antihistamine (41 FR 38312 at 38419). In the Federal Register of August 24, 1987 (52 FR 31892), FDA published a notice of proposed rulemaking on OTC antihistamine drug products that amended the tentative final monograph that was published on January 15, 1985 to include chlorcyclizine hydrochloride and doxylamine succinate as Category I OTC antihistamine active ingredients and to revise the proposed dosage for triprolidine hydrochloride. Interested persons were invited to file by October 23, 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 December 22, 1987

New data could have been submitted until August 24, 1988, and comments on the new data until October 25, 1988. No comments were received concerning chlorcyclizine hydrochloride or triprolidine hydrochloride. Therefore, final agency action on chlorcyclizine hydrochloride and triprolidine hydrochloride occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC antihistamine drug products.

With regard to doxylamine succinate, the agency received a technical report concerning a 2-year carcinogenicity and chronic toxicity study of doxylamine succinate in Fischer 344 rats and B6C3F1 mice that was conducted by the National Center for Toxicological Research (NCTR) under the auspices of the National Toxicology Program (NTP) (Ref. 1). The study was prompted by the National Cancer Institute's finding that methapyrilene, a similar antihistamine, is a potent liver carcinogen in the rat. The data on methapyrilene are on file in the Dockets Management Branch (address above) under Docket No. 75N-0244 and have been published (Ref. 2).

In the NCTR study (Ref. 1), doxylamine succinate was administered, ad libitum, as an admixture in the feed to male and female rats at dose levels of 0, 500, 1,000, or 2,000 parts per million (ppm) for 2 years. Mice of both sexes received food containing dose levels of 0, 190, 375, or 750 ppm. Each group contained 48 weanling animals per sex; the animals were scheduled for sacrifice at the end of 104 weeks. An additional group of animals (9 rats and 12 mice per sex) in each dose group was sacrificed at the end of 65 weeks. There were no significant treatment-related differences in survival in either rats or mice. In rats, the highest doxylamine succinate dose group had final body weights that were 22.8 percent (females) and 8.4 percent (males) lower than controls. A number of nonneoplastic lesions was observed in rats, including fatty change, degeneration, and hyperplasia of the liver and increased cytoplasmic alteration in the salivary glands. In mice, there was evidence of hepatotoxicity including hypertrophy, clear and mixed cell foci, and, in females, fatty change. There also was a treatment-related increase in "atypical" hepatocytes in male mice. Both male and female mice had a dose-related increase in thyroid follicular cell hyperplasia. There was a significant positive trend for increased incidence with increasing dose for both hepatocellular adenomas and carcinomas in male rats. When the

incidence of adenomas and carcinomas were combined, the trend test was positive ($p < 0.01$) and the incidence in the highest dose group was significantly ($p < 0.05$) increased over that of controls. No treatment-related increase in neoplasms was found in female rats. Although not statistically significant, one rat in each of the high dose groups of male and female rats was found to have a pineal gland tumor. Given the extreme rarity of this neoplasm in rats, these tumors may be reason for concern despite the lack of a statistically significant increase. In mice, doxylamine succinate administration produced an increased incidence of hepatocellular adenoma in both males and females. Also, both male and female mice had a treatment-related increase in follicular cell adenoma of the thyroid gland.

On June 13 and 14, 1991, the agency's Pulmonary-Allergy Drugs Advisory Committee met to discuss the results of the NCTR study. By a vote of five to one, the Committee concluded that the human carcinogenic potential of doxylamine is not likely. The Committee also recommended (again by a vote of five to one) that doxylamine remain OTC but that there be some warning to the consumer that these data exist (Ref. 3). The agency is currently evaluating the relevance of the study findings to humans and the advisory committee's recommendations. The agency will publish its final decision on doxylamine in OTC antihistamine drug products in a future issue of the Federal Register. At this time, drug products containing doxylamine succinate as an OTC antihistamine can remain in the marketplace with the labeling proposed for this ingredient in the tentative final monograph (52 FR 31892 at 31913 and 31914).

The agency's final rule, in the form of a final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is also being published in segments. Because the agency has completed its evaluation of all OTC antihistamine active ingredients other than doxylamine succinate, it is proceeding at this time with its final rule for products containing these ingredients. Final agency action on all OTC antihistamine drug products, except those containing doxylamine, occurs with the publication of this final monograph, which establishes §§ 341.3(g), 341.12, 341.72, and 341.90(e) through (q) for OTC antihistamine drug products in 21 CFR part 341. Combination drug products containing antihistamine ingredients are addressed in the tentative final monograph on OTC cough-cold

combination drug products, which was published in the Federal Register of August 12, 1988 (53 FR 30522). A final rule on combination drug products containing antihistamine ingredients will be published in a future issue of the Federal Register.

In the tentative final monograph published in the Federal Register of January 15, 1985, the agency discussed data submitted in support of the use of chlorpheniramine maleate in treating the symptoms of the common cold and, based on those data, proposed an indication for the temporary relief of runny nose and sneezing associated with the common cold in § 341.72(b) of the tentative final monograph (50 FR 2200 at 2203, 2204, and 2216). Recently, the agency has been evaluating applications requesting prescription-to-OTC switch for drug products containing antihistamines. Some have included labeling for use in the common cold without direct support from clinical studies. The requested claim is based on similarity of pharmacologic action to the other antihistamines included in the tentative final monograph for OTC antihistamine drug products, in which the agency proposed common cold claims based on clinical studies for chlorpheniramine maleate and the similarity of pharmacologic action of all the other monograph antihistamines (50 FR 2216). However, the agency has concerns whether the pharmacologic effects of older Category I ingredients that it considered previously as providing relief of common cold symptoms are characteristic of newer antihistamine drugs. The agency is presently evaluating whether data on chlorpheniramine maleate for this use should be extrapolated to other antihistamines included in this final monograph or any other antihistamines that may be switched from prescription to OTC status. Also, the agency is aware that there is controversy within the scientific community as to whether antihistamines are effective in treating symptoms of the common cold. Before completing this aspect of the rulemaking, the agency wishes to evaluate more recent clinical studies as well as the older data concerning the effectiveness of antihistamines in treating symptoms of the common cold. The agency will discuss these matters in a future issue of the Federal Register. Thus, the agency is deferring, at this time, a final conclusion concerning the use of antihistamines for the relief of sneezing and runny nose associated with the common cold, but is publishing its conclusions concerning

the use of antihistamines for allergic rhinitis.

The OTC drug procedural regulations (§ 330.10) 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).

As discussed in the proposed regulation for OTC antihistamine drug products (50 FR 2200), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the Federal Register. Therefore, on or after December 9, 1993, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule and amended proposed rule on OTC antihistamine drug products, 10 drug manufacturers, 1 drug manufacturers' association, 1 health care professional, 1 consumer group, and 8 consumers submitted comments. Copies of the comments are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since

publication of the proposed rule and amended proposed rule is also on display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the Federal Register of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

REFERENCES

- (1) Department of Health and Human Services, NCTR, "Technical Report for Experiments 406 and 407; Chronic Study of Doxylamine in Fischer 344 Rats and B6C3F1 Mice," 1991, included in OTC Vol. No. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817-819, 1980.
- (3) Transcript of the June 13-14, 1991 meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, Vol. II, pp. 172-182, in OTC Vol. No. 04HFM, Docket No. 76N-052H, Dockets Management Branch.

I. THE AGENCY'S CONCLUSIONS ON THE COMMENTS

A. General Comments on OTC Antihistamine Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings. The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the Federal Register of May 11, 1972 (37 FR 9464 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260); and in paragraph 2 of the preamble to the tentative final monograph for OTC cough-cold combination drug products, published in the Federal Register of August 12, 1988 (53 FR 30522 at 30524). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696-98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*,

487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment contended that antihistamines are not effective in alleviating the symptoms of runny nose or sneezing associated with the common cold and thus objected to the agency's decision that chlorpheniramine is effective for this use and that the data from the chlorpheniramine studies allow Category I status for this claim to be extended to all antihistamines. The comment contended that the studies upon which the agency based its decision (Refs. 1 and 2) are inadequate "to prove chlorpheniramine effective for treating colds" because the studies do not meet the standards of the Panel.

The comment described what it considered to be several major design flaws in the two studies. The comment maintained that neither study carefully excludes subjects with hay fever or other allergies from its study group and that the criteria (i.e., "cold symptoms for at least 24 hours, but not longer than 48 hours") for diagnosis of colds are weak. The comment stated that because the symptoms of hay fever mimic those of a cold and because antihistamines are effective in treating hay fever, careful exclusion of subjects with hay fever is essential in a study testing the effectiveness of antihistamines in treating colds. The comment asserted that the only effort made to exclude subjects with allergies was to ask whether they had known allergies. The comment stated that although the studies were conducted in the winter, in several cases they began as early as November or ended as late as May. The comment argued that both November and May are within the hay fever and allergy seasons. The comment suggested that the studies should have included only victims of known cold outbreaks or subjects with colds produced by virus challenge, or that, at the minimum, nasal eosinophil smears should have been done to exclude active allergies. The comment asserted that even a small number of subjects with hay fever could have skewed the study to benefit chlorpheniramine, "especially in view of the minimal effect that chlorpheniramine had."

The comment also alleged that one of the submissions to the agency (Ref. 1) excluded from its tables the results of one of its three investigators because these results were "inconsistent with the results of the other two studies." The comment maintained that if these studies are included, subjects taking chlorpheniramine are not significantly better off in most categories (e.g., patients' overall evaluation, total objective score, and physicians' global

evaluation) than subjects who took the placebo.

The comment added that the other study submitted to the agency (Ref. 2) only demonstrates minimal improvement in subjects taking chlorpheniramine because for each symptom (i.e., sneezing, runny nose, or nose blowing) the drug-treated subjects felt significantly better than those taking placebo at only one or two of the six measurement times.

Additionally, the comment asserted that one could not know how well subjects were randomized in these studies and that the bitter taste of chlorpheniramine could have confounded the results by foiling the double-blind design.

The comment cited two published reports that purported to demonstrate the ineffectiveness of antihistamines in "treating the common cold." One report reviewed 35 published studies of antihistamine use in colds and found that only 2 of the studies were well designed (Ref. 3). The comment noted that neither of these two well-designed studies supported the use of antihistamines to treat colds. The other published report cited by the comment involved a study of the effectiveness of two antihistamines in preventing or improving colds induced by inoculating volunteers with a cold virus. The comment concluded that the drugs were not beneficial because the severity of the colds and the duration of the symptoms were the same in both the drug-treated and the placebo-treated subjects (Ref. 4).

Noting that the overwhelming majority of cold preparations containing an antihistamine also contain a nasal decongestant, the comment suggested that the major flaw in both studies (Refs. 1 and 2) is that neither study demonstrates that the antihistamine adds to the effectiveness of the decongestant in treating colds. The comment maintained that although antihistamines alone may or may not have a small effect in decreasing sneezing and runny nose, this effect is likely to be overshadowed, if not lost, when an antihistamine is combined with a nasal decongestant. The comment added that because the two studies do not address the question of whether or not antihistamines add any benefit when they are used in combination "cold" drugs, the studies do not support the use of antihistamines as they are currently used in cold preparations on the United States OTC drug market. The comment also pointed out that under FDA's prescription drug review one antihistamine-nasal decongestant combination containing triprolidine hydrochloride and

pseudoephedrine hydrochloride was unable to be proven effective for the treatment of colds as a prescription drug, but that it is currently being promoted OTC almost exclusively for use in colds.

As discussed previously, the agency is deferring final action on this issue at this time.

References

- (1) Comment No. SUP004, Docket No. 76N-0052, Dockets Management Branch.
- (2) Comment No. SUP005, Docket No. 76N-0052, Dockets Management Branch.
- (3) West, S., et al., "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100-107, 1975.
- (4) Feller, A. E., et al., "The Failure of Antihistaminic Drugs to Prevent or Cure the Common Cold and Undifferentiated Respiratory Diseases," *The New England Journal of Medicine*, 242:737-744, 1950.

B. Comments on Switching Prescription Antihistamine Active Ingredients to OTC Status

3. One comment commended the agency for its initiative in proposing additional antihistamine active ingredients (dexchlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine hydrochloride, and triprolidine hydrochloride) for OTC status. The comment pointed out that dexchlorpheniramine maleate and dexbrompheniramine maleate are the dextrorotary isomers of drugs that have long been generally recognized as safe and effective. Adding that both ingredients have a long history of safe and effective use as prescription antihistamines, the comment noted that dexbrompheniramine maleate recently was switched to OTC use through the new drug application (NDA) process. The comment also stated that diphenhydramine hydrochloride and triprolidine hydrochloride have been safely and effectively used for years both as prescription and OTC drugs. The comment concluded that the inclusion of these four ingredients in proposed § 341.12 is a logical, correct, and justifiable action. On the other hand, another comment maintained that "more and stronger antihistamines" should not be available without requiring a physician's prescription.

In its report (41 FR 38312 at 38379 to 38396), the Panel concluded that several antihistamines, including diphenhydramine hydrochloride, that had previously been available only by prescription could be safely marketed OTC with appropriate labeling. Although the agency originally dissented from the Panel's Category I classification of diphenhydramine hydrochloride (41 FR 38313), in the

tentative final monograph for OTC antihistamine drug products, the agency concluded that diphenhydramine hydrochloride could be safely marketed OTC (50 FR 2200 at 2205). The agency also proposed that the antihistamines dexbrompheniramine hydrochloride, dexchlorpheniramine hydrochloride, and triprolidine hydrochloride, which had previously been available by prescription or for OTC marketing under NDA's, be generally recognized as safe and effective (50 FR 2205 and 2212 to 2214).

When considering whether or not a certain ingredient should be available OTC, the agency's primary concern is an assessment of the overall margin of safety. Factors included in the agency's determination of the margin of safety include toxicity, potential for harmful effects and collateral measures necessary for safe use, abuse and misuse potential, and the benefit-to-risk ratio. The agency has carefully evaluated the risk inherent in the OTC availability of antihistamines, including some ingredients that had been marketed OTC under approved NDA's for many years, and others that had been available only as prescription drugs. The agency concludes that, with appropriate labeling, the ingredients listed in § 341.12 of this final monograph are safe for OTC use within the dosage limits established in the monograph. The second comment did not submit any data demonstrating that these ingredients are not safe for OTC use, or that a physician's prescription is needed for their proper use. Based on adequate evidence establishing that these ingredients are generally recognized as safe and effective for OTC use as antihistamines, the agency is including dexchlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine hydrochloride, and triprolidine hydrochloride in § 341.12 of this final monograph.

4. One comment noted that the tentative final monograph for OTC antihistamine drug products lists diphenhydramine hydrochloride as Category I and suggested that the same status be accorded diphenhydramine monocitrate (now named diphenhydramine citrate). The comment pointed out that the agency concluded that the citrate salt could be considered identical to the hydrochloride salt in a notice of enforcement policy relating to diphenhydramine as a nighttime sleep-aid, which was published in the Federal Register on April 23, 1982 (47 FR 17740). Hence, the comment concluded that the diphenhydramine citrate dose equivalent to the diphenhydramine

hydrochloride dose should be classified Category I as an antihistamine.

A second comment (which was submitted to the agency prior to the publication of the tentative final monograph for OTC antihistamine drug products, but after the administrative record had closed), in the form of a citizen petition, also recommended that diphenhydramine be included in the antihistamine monograph as a Category I OTC antihistamine drug as both the hydrochloride and the citrate salts. In support of this recommendation, the petition stated that the Cough-Cold Panel had recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis at adult dosages of 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg daily, and at children's (6 years and over) dosages of 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg daily (41 FR 38312 at 38419). The petition presented a number of reasons why diphenhydramine could be considered safe and effective, as the hydrochloride salt and as the citrate salt, for use as an OTC antihistamine. These included: (1) The Panel's Category I recommendation for diphenhydramine hydrochloride; (2) diphenhydramine is a member of the ethanolamine class of antihistamines with clinical use dating to 1946; (3) the ingredient does not pose a serious safety question beyond its sedation qualities; and (4) proper labeling will minimize problems. A second citizen petition also requested that diphenhydramine citrate be included in the OTC antihistamine final monograph. The petition referenced agency statements in the rulemaking for OTC nighttime sleep-aid drug products (47 FR 17740 at 17741 and 54 FR 6814 at 6824) that the citrate salt could be considered identical to the hydrochloride salt.

The agency agrees with the first comment and the citizen petitions that diphenhydramine, in both the hydrochloride and the citrate salt forms, be included in the final monograph for OTC antihistamine drug products. The agency proposed in the antihistamine tentative final monograph (50 FR 2200 at 2204) that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine and proposed that diphenhydramine hydrochloride be Category I at an adult dosage of 25 to 50 mg every 4 to 6 hours for use in OTC antihistamine drug products (50 FR 2204). The agency confirms that proposal in this final monograph.

With respect to diphenhydramine citrate for use as an OTC nighttime

sleep-aid ingredient, the agency stated in the final rule for OTC nighttime sleep-aid drug products (February 14, 1989; 54 FR 6814 at 6823 and 6824) that diphenhydramine hydrochloride and diphenhydramine citrate are safe and effective. The agency concluded that the citrate salt could be considered identical to the hydrochloride salt, because the citrate salt is rapidly converted in the stomach to the hydrochloride salt. The agency also concluded that a dose of 76 mg diphenhydramine citrate is necessary to supply a diphenhydramine content equivalent to 50 mg diphenhydramine hydrochloride.

Therefore, the agency is including diphenhydramine citrate as an active ingredient in the antihistamine final monograph with the following directions: Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

The agency will also include directions for diphenhydramine citrate in the antihistamine final monograph under professional labeling as follows: Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

5. A health care professional had no real reservations about diphenhydramine hydrochloride being marketed OTC for treating allergic symptoms, but reported that an adult patient had committed suicide with an overdose of a drug product containing diphenhydramine hydrochloride.

The Panel, in its evaluation of whether a drug product is safe and effective for OTC use, considered the potential for misuse and abuse (41 FR 38312 at 38385) and did not find any data on diphenhydramine hydrochloride to warrant such concerns. Likewise, the agency at this time is not aware of any data to demonstrate that the misuse of diphenhydramine is a widespread problem. The agency is concerned about the possibility of any adverse effects resulting from the use of OTC drug products, but it also recognizes that a number of drugs in the marketplace (both OTC and prescription) can be and are knowingly misused by some individuals. However, the agency does not find that potential misuse by certain individuals should deprive the majority of the population from having OTC access to drugs that can be used safely and effectively when

labeled directions and warnings are followed. The agency has determined that the labeling and warnings required by this final monograph for OTC antihistamine drug products should provide for the safe and effective use of diphenhydramine hydrochloride when used at the monograph dosages. The agency concludes that diphenhydramine hydrochloride should be available as an OTC antihistamine because it is safe and effective when used as instructed in the labeling.

6. One comment contended that the agency's reasons for placing promethazine hydrochloride in Category III as a single ingredient in the tentative final monograph for OTC antihistamine drug products were in error. The comment stated that the agency's objections against OTC use of this ingredient are exclusively limited to the separate indication of temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies or allergic rhinitis. The comment urged the agency to recognize promethazine hydrochloride as a single entity as safe and effective for OTC use, at least for the indication pertaining to the temporary relief of runny nose and sneezing associated with the common cold. The comment argued that promethazine has been generally recognized as effective for a long time. The comment also alleged that the agency's rejection of general recognition of promethazine is based solely on the theoretical safety concern that use of this drug over an extended period of time to relieve symptoms of allergic rhinitis might result in tardive dyskinesia, a serious central nervous system syndrome that may persist indefinitely after discontinuation of the drug. The comment asserted that this safety concern does not exist because no case of tardive dyskinesia has ever been associated with promethazine use, and there has been a total lack of any adverse reports through the 34 years of continuous marketing of this drug in the United States. Further, although promethazine is structurally related to the other phenothiazine drugs which have been linked to causing tardive dyskinesia, the differences in chemical structures and pharmacological effects between promethazine and other phenothiazine drugs substantially lessen the possibility that promethazine could cause the range of side effects associated with other phenothiazine drugs. The comment concluded that the self-limiting use of promethazine to relieve symptoms of the common cold (7 to 14 days) negates the agency's safety

concern that extended use may cause tardive dyskinesia.

The Cough-Cold Panel classified promethazine hydrochloride in Category I as an OTC antihistamine (42 FR 38312 at 38390 to 38391). The agency dissented from the Panel's Category I classification of promethazine hydrochloride in the preamble to the Panel's report (41 FR 38313) based on the degree of drowsiness produced by promethazine hydrochloride and the possible adverse effects in children, such as extrapyramidal disturbances.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2206 to 2208), the agency stated that the possibility of choreoathetosis (a condition marked by jerky, involuntary movements) occurring with OTC oral doses of promethazine is unlikely and that there was no evidence to indicate that extrapyramidal side effects were more likely to occur with children. However, the agency placed promethazine hydrochloride in Category III as a single ingredient because of concerns that the rare, but serious adverse reaction of the central nervous system known as tardive dyskinesia might occur if promethazine is used on a long-term basis (50 FR 2200 at 2206 to 2208). The agency also stated that promethazine hydrochloride has not been used extensively as a single ingredient for antihistamine/allergic rhinitis/antiallergy use on a long-term basis. Data submitted to the agency were not sufficient to alleviate these concerns, and promethazine hydrochloride as a single ingredient was placed in Category III in the OTC antihistamine tentative final monograph.

In the tentative final monograph for OTC cough-cold combination drug products published in the Federal Register of August 12, 1988 (53 FR 30522 at 30558 to 30559 and 30563), the agency noted that promethazine has been widely used as a prescription drug, primarily in combination with other active ingredients for acute cough-cold symptoms on a short-term basis. At that time, the data and information indicated that such short-term use of promethazine hydrochloride in these products was safe and that under conditions of short-term use for the relief of cold symptoms, the possibility of tardive dyskinesia occurring was no longer a concern. Therefore, the agency proposed that promethazine hydrochloride in combination with other cough-cold and/or analgesic-antipyretic ingredients be Category I as an OTC antihistamine ingredient in combination drug products for short-term (7-day) use in relieving the

symptoms of runny nose and sneezing due to the common cold (53 FR 30563).

In response to the agency's decision to allow the OTC marketing of promethazine hydrochloride-containing cough-cold combination drug products for short-term (7-day) use for relief of the symptoms of the common cold, the Public Citizen Health Research Group (HRG) and the University of Maryland SIDS Institute (Ref. 1) submitted a citizen petition objecting to the OTC marketing of promethazine-containing cough-cold combination drug products. A number of physicians (Refs. 2 through 9) also objected to OTC status. The major concern that the petition and the physicians raised was that there is a possibility that the use of promethazine-containing drug products in children under 2 years of age may be associated with the occurrence of sudden infant death syndrome (SIDS) and that OTC availability of these drug products could "dramatically increase" "overuse" of these drug products in children in this age group. The petition also raised concerns about possible adverse neurological reactions associated with these drug products and about the use of prescription promethazine-containing drug products in children under age 2, in pregnant or nursing women, and in the elderly.

One manufacturer of promethazine-containing combination drug products submitted data and information to the OTC cough-cold combination drug products rulemaking in response to the concerns raised in the citizen petition, and has objected to the request of the petition (Ref. 10). In addition, the agency has received other information concerning OTC use of drug products containing promethazine hydrochloride in Canada (Ref. 11).

In response to the citizen petition and the manufacturer's submission, the agency scheduled a meeting of the Pulmonary-Allergy Drugs Advisory Committee on July 31, 1989, to discuss the advisability of switching the marketing of cough-cold combination drug products containing promethazine hydrochloride from prescription status to OTC status. Presentations were made by FDA staff and consultants, by representatives of Public Citizen Health Research Group, representatives of a major manufacturer of promethazine hydrochloride drug products, and by other interested persons. The agency has placed the transcripts of that meeting in the docket for the rulemaking for OTC cough-cold combination drug products (Ref. 12). Minutes of that meeting also will be included in that docket when available.

Presentations by FDA staff (Ref. 12) noted that adverse reaction reports from FDA's Annual Adverse Reaction Summaries since 1969 may not be adequate to establish incidence rates because of under reporting of reactions and the lack of a known number of patients receiving the product. It was also noted that because promethazine has been in use since 1951 and the agency did not begin computerizing its data base until 1969, that reporting of adverse reactions for this drug by that time would be at a minimal level because much was already known in the medical community about this drug's adverse reactions, which may cause a loss of interest in reporting reactions.

One case discussed involved a 27-year-old pregnant woman who was prescribed promethazine hydrochloride 25-mg suppositories, initially every 24 hours for 2 days and subsequently twice a day as needed, for persistent morning nausea and vomiting during her 12th week of pregnancy. After 3 days of use, she developed acute dystonic reactions that caused involuntary abnormal posturings of the neck, trunk, and left arm which lasted for about a year and a half. This case was considered unusual because promethazine was used for a very short time, i.e., 3 days, rather than on a long-term basis. Further, it was noted that although the treating physician initially diagnosed the condition as an acute dystonic reaction to promethazine, the long-term persistence of the condition (one and one-half years) qualified the diagnosis of the condition to be defined as both tardive dystonia and acute dystonia.

Manufacturer representatives in their presentations concluded that there was no real evidence of tardive dyskinesia (a condition primarily characterized by involuntary movement of the facial, buccal, oral, and cervical (neck) musculature (Ref. 13)) associated with promethazine use and that the case of the pregnant woman who developed dystonia (a condition that involves involuntary muscle clonic contortions characterized by abnormal sustained posturing of the neck, trunk, and extremities (Ref. 13)) after 3 days of therapy could have been idiosyncratic, and the condition may have been a movement disorder of pregnancy. The representatives stated further that the only reports of tardive dyskinesia with the use of promethazine occurred with patients using multiple neuroleptic drugs and occurred only after long-term use of phenothiazines. Therefore, short-term use would eliminate any risk of the occurrence of tardive dyskinesia.

After hearing the presentations, the Advisory Committee members voted on

a number of the issues presented. In response to the issue concerning the relationship between the use of promethazine-containing drug products and SIDS and/or sleep apnea, one committee member voted that no relationship exists, while the other seven members voted that there is a possible relationship. In response to the issue of whether there is a reason for concern about the use in the elderly of the proposed adult oral dosage of promethazine hydrochloride (6.25 mg every 4 to 6 hours, not to exceed 37.5 mg in 24 hours) on a short-term (7-day) basis, four committee members voted yes, and four members voted no. With respect to the potential neurologic toxicities at the proposed OTC dosage, none of the committee members felt there was a definite concern, but all voted that there are possible concerns. In response to the question (based on the data presented) concerning whether promethazine hydrochloride at proposed OTC doses with specific labeling requirements for short-term (7-day) use should be marketed OTC for relief of the symptoms of the common cold, the Committee recommended to FDA by a vote of seven to one that these drug products not be marketed OTC at this time.

In a notice in the Federal Register of September 5, 1989 (54 FR 36762), FDA concluded that it should accept the Advisory Committee's recommendations and announced that promethazine-containing combination drug products for use in treating the symptoms of the common cold may not be marketed OTC at this time. In that policy statement, the agency stated that before making a final decision concerning OTC status for these products and before responding to the citizen petition, that it intended to fully and thoroughly evaluate data and information submitted to date, data presented at the July 31, 1989 advisory committee meeting, and other data and information that may be pertinent. Additional comments and safety data have been submitted by a manufacturer of promethazine-containing drug products (Ref. 14). The submissions respond to issues raised at the July 31, 1989 advisory committee meeting and requests that combination cough-cold drug products containing promethazine hydrochloride be allowed to be marketed OTC.

Therefore, at the present time, the marketing status of promethazine-containing cough-cold drug products remains prescription only. After all the data and information have been reviewed and evaluated, the agency will publish its decision regarding the OTC

marketing status of combination drug products containing promethazine hydrochloride in a future issue of the Federal Register.

In prospective of that evaluation, the agency continues to believe that promethazine as a single ingredient has not been used extensively either to treat the symptoms of allergic rhinitis or the common cold and that unresolved questions remain concerning a causal role in tardive dyskinesia. In addition, presentations at the July 1989 advisory committee meeting regarding promethazine association with both acute and tardive dystonia and tardive dyskinesia reinforce the agency's concern that these conditions may occur with long-term use of promethazine hydrochloride at OTC dosages. Therefore, promethazine hydrochloride as a single ingredient is not being included in this final monograph. If, at a later date, promethazine is considered a monograph condition for use in OTC cough-cold combination drug products, the agency will reconsider its potential OTC use as a single ingredient antihistamine for the temporary relief of runny nose and sneezing associated with the common cold. This will be done in a future Federal Register notice in which the agency discusses the use of antihistamines for relief of the symptoms of the common cold or discusses the use of cough-cold combination drug products.

References

- (1) Comment No. CP, Docket No. 76N-052G, Dockets Management Branch.
- (2) Comment No. C00205, Docket No. 76N-052G, Dockets Management Branch.
- (3) Comment No. C00206, Docket No. 76N-052G, Dockets Management Branch.
- (4) Comment No. C00207, Docket No. 76N-052G, Dockets Management Branch.
- (5) Comment No. C00208, Docket No. 76N-052G, Dockets Management Branch.
- (6) Comment No. C00209, Docket No. 76N-052G, Dockets Management Branch.
- (7) Comment No. C00212, Docket No. 76N-052G, Dockets Management Branch.
- (8) Comment No. C00214, Docket No. 76N-052G, Dockets Management Branch.
- (9) Comment No. C00220, Docket No. 76N-052G, Dockets Management Branch.
- (10) Comments No. RC0001 and RC0002, Docket No. 76N-052G, Dockets Management Branch.
- (11) Comments No. LET 088 and LET089, Docket No. 76N-052G, Dockets Management Branch.
- (12) Transcripts of the July 31, 1989 meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, coded TR1, Docket No. 76N-052G, Dockets Management Branch.
- (13) *Drugs' Illustrated Medical Dictionary*, 27th Ed., W. B. Saunders Company, Philadelphia, 1988, s.v. "Anxiety" and "dyskinesia."

(14) Comments No. C00223, C00224, and C00225, Docket No. 76N-052G, Dockets Management Branch.

7. One comment requested that tripeleannamine hydrochloride be switched from prescription to OTC status, contending that this drug is nonaddictive and has no more harmful side effects than other "deregulated" (OTC) drugs. Noting that a number of antihistamines, including tripeleannamine hydrochloride, have a mild sedative effect, the comment stated that the side effects from some OTC drugs (such as alcohol, aspirin, acetaminophen, and dimenhydrinate hydrochloride) cause more harm to the abuser than tripeleannamine hydrochloride. The comment added that the benefits from the use of tripeleannamine hydrochloride outweigh any potential misuse or abuse of the drug. The comment mentioned that a number of common household substances from alcohol to household cleaners can be abused or misused, but this potential for abuse and misuse does not curtail the public's beneficial uses of these items. The comment added that tripeleannamine hydrochloride is marketed as an OTC drug product in Canada and there do not appear to be any unfavorable reports in the current literature. The comment pointed out that because antihistamines are often used for allergies for extensive periods of time, the cost factor to the consumer would be greatly reduced if tripeleannamine hydrochloride was marketed OTC.

Because no data concerning tripeleannamine hydrochloride were submitted to the Panel, it did not review this ingredient or make any recommendations on the safety or effectiveness of this drug for use as an OTC antihistamine. Although the comment presented some good reasons to support OTC status for this drug, unfortunately it did not provide any data concerning the safety and effectiveness of tripeleannamine hydrochloride for OTC use as an antihistamine. Therefore, the agency is not including tripeleannamine hydrochloride in this final monograph.

However, if appropriate safety and effectiveness data are submitted in accordance with the requirements of 21 CFR 330.10(a)(4), the agency will consider OTC status for this drug and a possible future amendment of this final monograph.

C. Comments on Specific OTC Antihistamine Active Ingredients

8. One comment requested that brompheniramine maleate be removed from OTC use based on information in

the "Handbook for Prescribing Medication During Pregnancy" (Ref. 1) that cited this ingredient as the only antihistamine associated with increased incidence of birth defects.

The agency believes that the statement that the comment refers to was cited in the above reference as "A large-scale study of drugs that could possibly have a teratogenic effect * * * included chlorpheniramine, pheniramine, and brompheniramine. Of these, only with brompheniramine was there a statistically significant increased risk of teratogenicity." Based on a review of the references cited in the "Handbook for Prescribing Medication During Pregnancy," the agency believes that the large-scale study referenced was a study by Heinonen, Slone, and Shapiro (Ref. 2). The agency has reviewed this study and concludes that a causal association between the use of brompheniramine maleate during pregnancy and the occurrence of birth defects has not been established.

The Heinonen, Slone, and Shapiro study (Ref. 2) is a retrospective study of 50,282 mother-child pairs that included 3,248 malformed children and that considered the relationships between the occurrence of birth defects during the first 4 months of pregnancy and the exposure to antinauseant, antihistamine, and phenothiazine drug products. The agency notes that some of the exposure times reported in this study may not be precise. In this study, the relative risks for occurrence of malformations are presented as crude values, values standardized for hospital variability, and values standardized for the mother's ethnic group and for survival of the child.

In one analysis, the investigators considered all 3,248 malformed children in relation to exposure to the entire group of antinauseants, antihistamines, and phenothiazines in the first 4 lunar months of pregnancy. Out of 65 mother-child pairs with exposure to brompheniramine, they found 10 children with malformations. Based on these data, the investigators stated that brompheniramine was the only drug that had an estimated relative risk that was statistically significant at the 0.05 level. The investigators added that this was the only drug for which the relative risk was greater than 1.5. However, when the investigators analyzed the data confined to the 2,277 children who had malformations which were uniformly distributed across the hospitals studied, they found a hospital-standardized relative risk of 1.98 (6 malformed infants in 65 exposed mother-child pairs) for brompheniramine. The agency believes

that, if the small sample size is taken into consideration and an adjustment were made to account for the large number of associations tested (i.e., analysis of multiple drug categories and multiple types of birth defects) involved in the study, these standardized relative-risk findings would not be considered statistically significant based on the increased probability that the findings in this study may have occurred by chance.

The data presented by Heinonen, Slone, and Shapiro are from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke. The agency obtained a printout of the Collaborative Perinatal Project pertaining to brompheniramine exposure in the first 3 lunar months of pregnancy (Ref. 3). This printout shows that during the first 3 lunar months of pregnancy, birth defects occurred in 4 children out of 22 mother-child pairs exposed to brompheniramine. The structural birth defects were syndactyly (two cases), polydactyly, and pectus excavatum. Because it is generally accepted that the development of these structural malformations occurs in the first 3 lunar months of pregnancy and exposure to the drug during the fourth lunar month would not cause a structural birth defect (Refs. 4 and 5), the agency concludes that the two structural malformations mentioned by Heinonen, Slone, and Shapiro (Ref. 2) as occurring in mother-child pairs in the fourth lunar month are probably related to environmental factors or genetic factors or may be due to chance. In addition, the agency notes that all mothers of the four malformed children who were exposed to brompheniramine during the first 3 lunar months of pregnancy were also exposed to one or more other medications (Ref. 3).

The Heinonen, Slone, and Shapiro study was an exploratory investigation of several drugs and several possible adverse events. An exploratory study may identify possible associations and suggest areas for further study. However, without advance credibility of specific associations, an exploratory study is not the proper mechanism for confirming such associations. The agency concludes that an association cannot be confirmed from the same data set that suggested the association in the first place.

For the above reasons, this study does not establish a definite association between brompheniramine exposure and birth defects. The agency recognizes that this does not rule out the possibility that this association exists, but concludes that such an association is

not supported by the study. In addition, Heinonen, Slone, and Shapiro do not make any statement specifically about brompheniramine teratogenicity and conclude that there was essentially no association between uniform malformations and the large categories of drug groups studied and that "there was no evidence to suggest that exposure to antihistamines * * * was related to malformations overall, or to large categories of major or minor malformations."

Based on the above information, the agency concludes that this study does not demonstrate that brompheniramine maleate is a teratogen. Further, the agency is not aware of any other studies that would establish a causal association between the use of brompheniramine maleate and birth defects. Thus, the agency believes that brompheniramine maleate when labeled with the pregnancy/nursing warning required in 21 CFR 201.63 is safe for OTC use and is including this ingredient in this final monograph.

References

- (1) Berkowitz, R. L., D. R. Coustan, and T. K. Mochizuki, "Antihistamines (over-the-counter): Brompheniramine, Chlorpheniramine, Cyclizine, Doxylamine, Meclizine, Phenindamine, Pheniramine, Pyrilamine," in "Handbook for Prescribing Medications During Pregnancy," 1st Ed., Little, Brown and Co., Boston, pp. 24 and 26, 1986.
- (2) Heinonen, O. P., D. Slone, and S. Shapiro, "Antinauseants, Antihistamines, and Phenothiazines," in "Birth Defects and Drugs in Pregnancy," Publishing Sciences Group, Inc., Littleton, MA, pp. 322-334 and 475, 1977.
- (3) Excerpts of data from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke and Boston University, 1981, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Shepard, T. H., "Catalog of Teratogenic Agents," 5th Ed., The Johns Hopkins University Press, Baltimore, p. xvii, 1986.
- (5) Tuchmann-Duplessis, H., and P. Haegel, "Volume 2 Organogenesis," Springer-Verlag, New York, pp. 2-11, 1974.

9. One comment submitted data (Ref. 1) to support reclassification of phenyltoloxamine citrate from Category III to Category I at an adult dose of 30 to 60 mg every 4 to 6 hours, not to exceed 360 mg in 24 hours, and at a children's (ages 6 to 12 years) dosage equal to one-half the adult dose. The submitted data consisted of two clinical studies (Ref. 1) and a published pharmacology study (Ref. 2).

The agency has reviewed the submitted data and other information and determined that the data are not sufficient to establish the effectiveness

of phenyltoloxamine citrate as an OTC antihistamine. The agency finds that the study design of the two clinical studies (CRD 85-17 and 85-18) is flawed, and the studies were not adequately controlled.

Study CRD 85-17 was a double-blind, parallel, placebo-controlled study involving 108 subjects ranging in age from 18 to 59 years with a confirmed diagnosis of seasonal allergic rhinitis. The study was designed to assess the antihistaminic effectiveness of phenyltoloxamine citrate in the treatment of seasonal allergic rhinitis. Subjects were randomized into one of three treatment categories: those taking the 30-mg test product, those taking the 60-mg test product, and those taking the placebo, for a 1-week period at a dosage of one capsule four times a day at 8:30 a.m., 12:30, 5:00, and 10:00 p.m. Measurement of the relief of symptoms was done in two ways: on days 1, 2 and 8, the symptoms were evaluated hourly from 8:30 a.m. to 4:30 p.m. at the study site by an investigator and the subject; on days 3 to 7, the effect of the test product on symptoms was evaluated by the subjects at home on four occasions (morning, noon, evening, and bedtime) and recorded in a diary.

The study results divide subjects into two groups: those who missed a dose of study medication and those who had to take rescue medication. These differences in the study subjects were subsequently ignored, and the two groups were combined (and included in the analysis of the results of this study) and considered as being similar. Even though the total number of each test group of subjects who missed a dose or took rescue medication was similar, there were differences in the number of subjects who had missed a dose versus those who took rescue medication in each group as follows: in the 30-mg dose group, three subjects took rescue medication and two subjects missed doses; in the 60-mg dose group, three subjects took rescue medication and three subjects missed doses; while in the placebo group, five subjects took rescue medication and one subject missed doses. In addition, there was a variance in the total number of days and dosage interval doses that were missed as well as when the rescue medication was taken. The agency believes that these differences should have been noted and considered in the analysis of the data rather than combined and ignored.

In analyzing this study, the agency noted considerable variation in the test results of the effect of the 30-mg drug product on symptom relief, which may be due to operative variables such as

variations in pollen counts and humidity that were not considered in the methodology of the study. For example, for the relief of nasal congestion, the data indicated that the active drug ingredient was more effective than the placebo on day 1 (at three observation points), on day 2 (at six points), and on day 8 (at five points). While these differences were between the lower 30-mg dose of the active drug and the placebo, the data show that at several of these same observation points this lower dose was more effective than the higher 60-mg dose of the drug. On days 4, 6, and 7, the difference between regimens (also in favor of the lower dose of active drug) was only apparent at one observation point. On days 3 and 5, no differences were noted. On days 2 and 8, there were 12 observation points, while on the other days, there were only 4 observation points. On days 2 and 8, the subjects remained indoors for 8 hours, while on days 3 through 7, the subjects were not confined and their whereabouts were not stated. Although statistical methods were not mentioned in detail, observation points were compared with baseline mean values and days were compared to days. Irrespective of the results, even if differences were demonstrated, it would be difficult to determine whether they were attributable to drug effect, a variation in the pollen count, humidity, or the effect of a controlled versus an uncontrolled environment. The agency believes that a comparison of effects for site days and a separate comparison of nonsite days would have reduced the uncontrolled operative variables.

The agency also found that differences between the three treatment groups with respect to relief of the symptoms of allergic rhinitis were not consistently demonstrated and were erratic. Further, on those days when differences were noted, it was difficult to determine whether the results were due to drug effect or the inadequacies of the study design and analysis. Phenyltoloxamine citrate was shown to be more effective than the placebo (i.e., with a statistically significant p value of 0.05 or less) on only one day (day 2) for relieving both wet and itchy symptoms. Further, on only a few occasions was the higher 60-mg dose of active drug more effective than the placebo. In addition, the lower 30-mg dose of active drug was found to be superior to both the higher 60-mg active drug dose and to the placebo. When the effects of the drug on wet and itchy symptoms were combined, the agency finds that statistically significant differences were recorded for only 3 out of the 59

observation points (on day 2 at 2:30 p.m., on day 6 at bedtime, and on day 7 in the morning). The data for nasal flow measurements demonstrated that on only one day was the 30-mg dose more effective than the 60-mg dose. In addition, the placebo appeared to be more effective than the 60-mg dose. Thus, the nasal flow measurements were not very helpful.

The protocol for study CRD 85-18 was essentially identical to study CRD 85-17 with the exception that there were 74 subjects who participated in the study. Other minor variations between the two studies included the following: (1) analysis of the data was done by comparing the effect of the active drugs and placebo on relieving the symptoms by days at study site, days at home, and by combining study site days and home site days, whereas study CRD 85-17 compared observation points on each day and overall days, and (2) a different grading system was used to record symptoms of a stuffy nose and the methodology of performing or recording nasal airway resistance. The second evaluation day was staggered over a 4-day period (either day 2, 3, 4, or 5), while in study 85-17, day 2 was always the second 8-hour evaluation day. The agency believes that these differences would tend to bias the results in favor of the active drug because there are less points of comparison in this study and the additional 3-day period would create a steady state condition. Even the comment concluded that the data were not supportive of any demonstrable efficacy for the active drug. The reported results of the study confirm this conclusion.

The agency disagrees with the comment's explanation of study CRD 85-18 and its contention that this study is incomplete and therefore inconclusive. The number of subjects recruited (74) for the study was adequate to demonstrate efficacy. In addition, carrying out the study over two allergy seasons (spring and fall) is not a reason to reject the study because symptoms of allergic rhinitis were required for entrance into the study. Also, the complexity of the case report forms for study CRD 85-18 was not greater than the complexity of the case report forms for study CRD 85-17, and thus is not a reason to reject the study. In fact, the design of study CRD 85-18 may have introduced bias into this study in favor of the active ingredient rather than the control, because steady state would more likely have been achieved on the staggered second evaluation day schedule that was used in this study.

The published study by Falliers et al. (Ref. 2) and the pharmacology study (Ref. 3) reviewed by the agency in the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2208) are the same study. The agency stated in the tentative final monograph that this study demonstrated that there is a statistically significant difference between the pharmacologic action of a placebo and phenyltoloxamine citrate in favor of the active ingredient at 1- and 2-hour intervals after a single dose has been given. However, the study did not demonstrate the effectiveness of phenyltoloxamine over a long enough period of time that would be representative of the actual conditions under which the drug would be used. The agency stated that additional data from multiple-dose clinical studies carried out over a period of at least 1 week, and including an adequate number of patients per dose level of test ingredient and placebo, demonstrating the effectiveness of phenyltoloxamine would be necessary to reclassify this active ingredient in Category I. The agency's conclusions regarding that study remain the same. Further, the results of studies CRD 85-17 and 85-18 do not alter the agency's clinical opinion that these studies do not adequately support the effectiveness of phenyltoloxamine citrate as an OTC antihistamine.

Based on a lack of adequate clinical efficacy data, the agency concludes that phenyltoloxamine citrate should not be upgraded to monograph status. Therefore, this ingredient is not being included in this final monograph.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 4).

References

- (1) Comments No. RPT003 and RPT004, Docket No. 76N-052H, Dockets Management Branch.
 - (2) Falliers, et al., "Inhibition of Cutaneous and Mucosal Allergy with Phenyltoloxamine," *Annals of Allergy*, 41:140-144, 1978.
 - (3) Comments No. C00168, LET003, and SUP007, Docket No. 76N-0052, Dockets Management Branch.
 - (4) Letter from W. E. Gilbertson, FDA, to E. H. Hanus, Richardson-Vicks, coded LET085, Docket No. 76N-052H, Dockets Management Branch.
10. One comment described personal experience in using several different antihistamines, including methapyrilone hydrochloride and pyrilamine maleate, for self-treatment of hay fever. The comment stated that these drugs worked well but noted that methapyrilone hydrochloride had been

removed from the market because it was a potent carcinogen in animal tests. The comment stated that it did not find pyrillamine maleate listed in the tentative final monograph and questioned whether pyrillamine maleate is similar to methapyrilene and whether it has been tested as cancer-causing.

The agency concluded in the tentative final monograph, based on data provided in a National Cancer Institute study, that methapyrilene is a potent carcinogen in animals and must be considered a potential carcinogen in man (50 FR 2200 at 2202). The agency initiated a recall of all oral and topical products containing methapyrilene and placed methapyrilene fumarate and methapyrilene hydrochloride in Category II (50 FR 2202). Thus, methapyrilene was not included in the tentative final monograph. However, pyrillamine maleate was proposed as a Category I antihistamine in the tentative final monograph (50 FR 2216).

Because of the similarity in chemical structure between pyrillamine and methapyrilene and because of the extensive use of pyrillamine maleate in both prescription and OTC drug products, it was nominated for testing by NCTR, under the auspices of the NTP (Ref. 1). Studies, in which pyrillamine was tested in rats and mice in chronic (104 weeks) bioassays, were completed in February and March 1987 and preliminary findings indicated no cancer-causing potential (Ref. 2). The final report was published in June 1991 with the conclusion that there was no evidence for a carcinogenic response to pyrillamine maleate by either F344 rats or B6C3F1 mice (Ref. 3). Based on the above information, the agency concludes that pyrillamine maleate is safe for OTC use and is including this ingredient in this final monograph.

References

- (1) "Final Report—90 Day Subchronic Study Report on Pyrillamine in Fischer Rats," paragraph 1.0, Introduction, NCTR, Jefferson, AR, page 5, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Memorandum of telephone conversation between G. Kerner, FDA, and W. Allaben, NCTR, January 27, 1989, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Department of Health and Human Services, NTP, "Technical Report for Experiment No. 408 and 409 (NTP Experiments 05013-03 and 05013-04); Pyrillamine: 104 Week Chronic Dose Study in Rats, and Pyrillamine: 104 Week Chronic Dose Study in Mice," June 1991.

D. Comments on Dosages for OTC Antihistamine Active Ingredients

11. Two consumers questioned the safety of a higher dosage of

chlorpheniramine maleate than previously permitted for OTC use. One consumer stated that a higher dosage of chlorpheniramine maleate may cause reactions and any antihistamine should be tested properly before the public is allowed to self-administer the product. Another consumer stated that the agency should warn against the overuse of OTC antihistamines. The consumer did not further elaborate on what was meant by the term "overuse."

The Panel reviewed extensive test data on antihistamine active ingredients, including chlorpheniramine maleate. The Panel recommended that a number of antihistamines could be generally recognized as safe and effective for OTC use in specified dosages and with specific labeling. In general, the agency has concurred with the Panel's recommendations.

Based on its review of clinical data on chlorpheniramine maleate, the Panel recommended that this ingredient be available OTC at a dosage that was twice that previously permitted for OTC use (41 FR 38312 at 38383). The Panel made this dosage recommendation because it found that chlorpheniramine maleate had not been shown to be effective for adults at a dose less than 4 mg. (The Panel recommended that the dose for children 6 to under 12 years of age be one-half the adult dose.) The Panel's proposed OTC dosage was as follows: adults, 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours; children 6 to under 12 years of age, 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours. The Panel noted that the chief side effect of chlorpheniramine maleate is sedation and recommended an appropriate warning, "May cause drowsiness." The Panel also recommended warnings that would inform the consumer to avoid driving a motor vehicle or operating heavy machinery and to avoid alcoholic beverages while taking a product containing this drug.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200), the agency concurred with the Panel's determination that an adult dose of less than 4 mg chlorpheniramine maleate is not effective (50 FR 2205) and that extensive data support the safety and effectiveness of the higher dosages for chlorpheniramine for OTC use (50 FR 2208). Further, the agency proposed a revised warning concerning the drowsiness effect of antihistamines to include sedatives and tranquilizers in addition to alcohol as drugs that may intensify the drowsiness effect of antihistamines (52 FR 31913).

With regard to warnings concerning the overuse of OTC antihistamine drug products, the agency believes that the required labeling set forth in this final monograph is adequate to provide for the safe and effective use of these products. Antihistamines have been used OTC for many years for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis), which may be seasonal as well as perennial. It is generally recognized that these drugs are safe for their intended use under monograph conditions, even when used over extended periods of time and that the warnings required by this monograph would adequately address any concerns regarding any significant side effects that could occur.

A concern about two antihistamines being taken simultaneously was addressed in the tentative final monograph (50 FR 2203). The agency stated that it recognized that many products containing antihistamines for relieving symptoms of hay fever and the common cold are available in the OTC drug marketplace, but is unaware of any specific information that would raise health concerns about these products being marketed OTC under the conditions stated in the monograph. Because each product is required to be prominently labeled with the product's statement of identity, i.e., "antihistamine" (21 CFR 201.61), consumers are provided adequate information that these products contain an antihistamine drug. By reading the labels, consumers are informed that different drug products contain an antihistamine intended to treat the same symptoms. Thus, the agency believes that the likelihood that such products would be taken simultaneously is very low.

The agency therefore concludes that the warnings and directions set forth in this final monograph should provide for the safe and effective OTC use of antihistamine drug products and at this time there is no need to expand the monograph to include additional warnings against overuse of these products.

E. Comments on Labeling of OTC Antihistamine Drug Products

12. Two comments stated that FDA lacks statutory authority to prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and to prohibit alternative labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. One comment recommended that instead of prohibiting the use of alternative truthful terminology, FDA should

permit manufacturers to choose consumer oriented language to communicate the desired label indications, so long as such language is not false or misleading. Both comments noted that FDA proposed certain revisions to the "Exclusivity Policy" on April 22, 1985 (50 FR 15810) and stated that they would submit further comments on that proposal.

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

13. One comment stated that the numerous pharmacological properties of diphenhydramine should permit a sleep-aid claim for this ingredient when it is used as an antihistamine. The comment noted that diphenhydramine has previously been classified Category I as a nighttime sleep-aid and requested that this type of claim be permitted in addition to the allowable antihistamine claims.

After this comment was submitted, the agency addressed the issue of "multi-use" labeling, i.e., labeling a drug product with some or all of the proven pharmacologic activities of the drug whether or not the conditions to be treated are related, in another segment (tentative final monograph) of the rulemaking for OTC cough-cold combination drug products (53 FR 30522 at 30551 to 30552). In that

segment of the rulemaking for these drug products, the agency stated that there is no legal restriction that prevents multi-use labeling. For products that contain an ingredient with multi-use labeling, the labeling for each "different" use of the ingredient would have to be distinct and not confusing and would have to meet the requirements of the applicable OTC drug monographs in part 330 and the labeling requirements for OTC drugs in subpart C of 21 CFR part 201.

Thus, the manufacturer would need to provide labeling for all Category I intended uses in such a manner that the labeling for each approved indication that the manufacturer chooses to promote is distinct and not confusing. Labeling should be written so that consumers may readily understand the indications, directions for use, and warnings for each intended use. Further, the labeling must provide adequate information to prevent the possibility of overdosing and misuse when multiple and/or overlapping symptoms are self-treated.

As stated in the cough-cold combination drug products tentative final monograph, because of the labeling requirements and the need to provide information that is not confusing to consumers, the agency invites manufacturers to consult with it before labeling their OTC drug products with multi-use labeling.

14. One comment requested that the phrases "temporarily relieves" (proposed in the antihistamine tentative final monograph) and "for the temporary relief of" (proposed in the nasal decongestant tentative final monograph) be interchangeable.

The agency agrees with the comment. Because the phrases "for the temporary relief of" and "temporarily relieves" are interchangeable, the agency is including the option of using either phrase in the indications included in § 341.72(b) of this final monograph.

15. Three comments requested that manufacturers be allowed to use either of the indications proposed in § 341.72(b)(1) and (2) rather than be required to use both indications in the labeling of antihistamine drug products. The comments contended that an antihistamine product promoted primarily for a specific indication, i.e., for the common cold or for hay fever, should be allowed to use only the corresponding indication in its labeling. Two of the comments stated that the consumer market to whom allergy products are directed is different than the consumer market using cold products and that having both indications on the same product would

confuse consumers looking for a product for only one of the specified indications. One comment added that, in its view, it is inappropriate to include allergy and hay fever indications in the labeling of an OTC combination drug product intended to be used for relieving symptoms of the common cold. The comments concluded that the wording of proposed § 341.72(b) should be changed from "limited to both" to "limited to one or both" (of the indications).

The agency agrees with the comments' arguments that for some OTC antihistamine-containing drug products it would be inappropriate to include both the allergy and common cold indications in the labeling. Where an antihistamine drug product is marketed generally as an antihistamine, it is beneficial to consumers to have all of the indications stated in the product's labeling, and manufacturers are encouraged to do so. However, when an antihistamine drug product is marketed for a specific target population (e.g., allergy sufferers) or when the antihistamine is present in a combination drug product marketed for a different specific target population (e.g., cold sufferers), the agency does not find that it is necessary for the products to be labeled with both the allergy and the common cold indications. The agency is addressing "allergy" indications only in this final rule and will respond to the comments' requests in a future issue of the Federal Register when a final decision is made on the use of antihistamines for symptoms of the common cold.

16. One comment submitted two consumer surveys to demonstrate that substantial numbers of consumers recognize that relief of "post-nasal drip" is a desirable end benefit and consequence of the use of OTC drug products containing antihistamines which, through their drying (anti-secretory) actions, relieve symptoms of sinus congestion and allergic rhinitis (hay fever) and, furthermore, that consumers clearly understand the term "post-nasal drip." The comment requested that indications pertaining to "post-nasal drip," i.e., "Helps (relieve, alleviate, decrease, reduce or dry up) post-nasal drip" be included in the final monograph for OTC antihistamine drug products and for OTC cough-cold combinations containing antihistamines.

The agency has reviewed the comment and other information and determined that the consumer surveys do not demonstrate the effectiveness of OTC antihistamine drug products in relieving "post-nasal drip." The two

consumer mail panel studies were designed to investigate consumer attitudes towards, and usage of, sinus and hay fever remedies. The agency notes that the comment stated that of the 263 responding sinus sufferers, 49 percent (129) considered relief of post-nasal drip important when choosing a sinus remedy. Similarly, 48 percent (119) of the 248 hay fever respondents indicated that relief of post-nasal drip was important when consumers choose a hay fever product.

The Panel referred to "checking post-nasal drip" as an unsubstantiated labeling claim unless studies specifically designed to assess this activity were presented (41 FR 38312 at 38415). The Panel did not assess this claim for antihistamines, but placed the claim in Category III for nasal decongestants. The Panel stated that studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

The submitted consumer surveys were not designed to demonstrate the effectiveness of OTC antihistamine drug products in relieving the symptom "post-nasal drip." In addition, the surveys do not define the term "post-nasal drip" or the ability of consumers to recognize specific symptoms that would allow them to determine whether they were experiencing "post-nasal drip." The consumer surveys do not demonstrate understanding of the term "post-nasal drip" or provide a basis for a "post-nasal drip" indication.

The agency has not approved a "post-nasal drip" claim in any new drug application for an antihistamine drug product. Clinical studies specifically designed to demonstrate the effectiveness of antihistamines in relieving "post-nasal drip" would be necessary before this claim could be used in the labeling of any antihistamine drug product. Such studies should be designed to evaluate the symptoms of "post-nasal drip" in terms of specific symptoms that can be recognized by consumers as "post-nasal drip." The agency suggests that any party interested in studying the use of an antihistamine for this claim meet with the agency to discuss an appropriate protocol before beginning the study. For the above reasons, indications pertaining to "post-nasal drip" are not being included in this final monograph for OTC antihistamine drug products.

17. Noting that, in the tentative final monograph (50 FR 2200 at 2203), the agency proposed to exclude "sinus congestion" as an approved indication for single-ingredient antihistamine drug

products, one comment requested that "sinus congestion" be an approved indication for combination drug products containing an oral nasal decongestant and an antihistamine. The comment noted the Panel's recommendation that "any single [Category I] antihistamine * * * may be combined with any [Category I] single oral nasal decongestant active ingredient * * *" (41 FR 38312 at 38420) and urged FDA to adopt this recommendation and to include "sinus congestion" as an approved indication for such combination drug products.

The agency reaffirms its conclusion as stated in the tentative final monograph that data have not demonstrated that antihistamines are effective in the treatment of "sinus congestion." Therefore, such claims for single-ingredient OTC antihistamine drug products are not included in this final monograph.

In § 341.80(b)(2) of the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220 at 2238), the agency proposed the following indications that refer to sinus congestion for nasal decongestant drug products:

(iv) "Helps decongest sinus openings and passages; relieves sinus pressure."

(v) "Promotes nasal and/or sinus drainage; relieves sinus pressure."

In the tentative final monograph for OTC cough-cold combination drug products, the agency proposed that combination drug products containing an oral nasal decongestant and an antihistamine be Category I (53 FR 30522 at 30561). Such combination drug products can be labeled with the indications that are applicable to each pharmacologic group included in the combination. Therefore, under the tentative final monograph for OTC nasal decongestant drug products (50 FR 2238) and the tentative final monograph for OTC cough-cold combination drug products (53 FR 30561 to 30562), combination products containing a Category I oral nasal decongestant and a Category I antihistamine can be labeled with indications relating to "sinus congestion."

18. One comment objected to the proposed elimination of the term "Caution(s)" in the labeling of OTC drug products. The comment contended that "Warnings" are harsher (stronger) and more serious than "Cautions" and even preclude use of a product under certain conditions. The comment stated that a "Caution," on the other hand, does not preclude use unless something occurs during use; but it often alerts the consumer to a potential problem. The comment added that a caution may also

address a monitoring function to be performed while the product is in use. The comment felt that it is important for the consumer to be able to distinguish between precautionary statements and more serious warnings. Also, because the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the comment stated that flexibility to use both terms is essential in order to prepare accurate and comprehensible labeling.

Another comment suggested that the agency differentiate between "Warnings," "Cautions," and "Precautions" in OTC drug product labeling. The comment stated that the term "Warning" is the strongest of the terms and should be taken the most seriously. The comment contended that the term "Caution" should be used to convey important information related to the safe and effective use of the product but which allows for judgment on the part of the user, e.g., "This product may cause drowsiness." The comment felt that it undermines the importance of a "Warning" section if it contains too much information or if it includes less than serious language. The comment provided examples of the types of information that it considered appropriate as warnings and cautions for products containing the maleate salts of brompheniramine, chlorpheniramine, dexbrompheniramine, and dexchlorpheniramine.

Section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling " * * * such adequate warnings * * * as are necessary for the protection of users * * * ." Section 330.10(a)(4)(v) of the OTC drug regulations (21 CFR 330.10(a)(4)(v)) provides that labeling of OTC drug products should include " * * * warnings against unsafe use, side effects, and adverse reactions * * * ."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information. In addition, the term "precaution(s)," as in "Drug Interaction Precaution(s)" is often used in OTC drug monographs, but is listed under "Warnings" as, for example, in the rulemakings for OTC nasal decongestant drug products and OTC

bronchodilator drug products. (See the Federal Register of January 15, 1985 (50 FR 2220 at 2239) and October 2, 1986 (51 FR 35326 at 35339), respectively.)

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. The agency is not convinced that consumers will make the distinctions between "warnings" and "cautions" that the comments have made. Further, the agency does not believe that the importance of the "Warnings" section will be undermined if all of the information about unsafe use, side effects, and adverse reactions is presented under a single heading. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. However, except in instances where the agency has stated that a particular warning statement must appear as the first warning after the "Warnings" heading, the agency has no objections if manufacturers list the various warnings statements in their order of preference, e.g., listing first those they consider more serious followed by those they consider to be less serious statements. Drug interaction precaution information will continue to be listed under the heading "Drug Interaction Precautions" as part of the warnings information.

19. One comment stated that the Panel made a factual error in the number of subjects in a study (Ref. 1) mentioned in its discussion of phenindamine tartrate (41 FR 38312 at 38388). The Panel's report stated that 250 subjects were in the study, whereas the article (Ref. 1) indicated that 1,589 subjects were observed. The comment contended that this large discrepancy in the number of subjects in the study is significant with respect to the validity of the study data on the frequency of stimulation or drowsiness and thus phenindamine tartrate should be exempt from the Panel's proposed warning regarding the occurrence of drowsiness as a side effect. [Note: This comment was submitted after the administrative record following publication of the advance notice of proposed rulemaking closed and thus was not discussed in the tentative final monograph.]

The agency has reviewed the discrepancy described by the comment and agrees that the correct number of subjects in the study is 1,589, not 250 as mentioned in the Panel's report. Although the agency is unable to ascertain how the number 250 appeared in the Panel's report, it appears that the Panel based its conclusions on the study's actual findings that 3 percent (51) of the 1,589 subjects experienced drowsiness and 12 percent (196) of the 1,589 subjects experienced stimulation. (See Table II at page 478 of Ref. 1.) Based on these percentages and the number of subjects, the agency agrees with the Panel's conclusion that "data that would establish the frequency of stimulation or drowsiness among those taking the drug in recommended dosages are inadequate and cannot be used for making phenindamine an exception with respect to a warning regarding the occurrence of drowsiness as a side effect" (41 FR 38388). The comment did not submit additional data to support an exemption from this warning for phenindamine tartrate. Therefore, the warning "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery," in § 341.72(c)(3) of the final monograph is required for OTC antihistamine drug products containing phenindamine tartrate.

Reference

(1) Loveless, M. H., and M. Dworin, "Allergy and Antihistamine Therapy. A Review," *Bulletin of the New York Academy of Medicine*, 25:473-487, 1947.

20. Several comments stated that it is difficult to read labels of antihistamine drug products because the print on the labels is small. The comments were particularly concerned that the required warnings would not be legible and thus could lead to adverse use of the product. The comments requested larger print size and greater prominence of warnings on antihistamine drug products. One comment added that most OTC antihistamine products are very repetitious in their warning labeling and recommended bold lettering or a colored label to enhance warning statements.

The agency believes that the labeling proposed in this final monograph includes only essential information that is necessary to assure proper and safe use of OTC antihistamine drug products by consumers. Moreover, the labeling of

drugs must comply with section 502(c) of the act (21 U.S.C. 352(c)) which states that a drug shall be deemed to be misbranded "If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use."

When an OTC drug product is packaged in a container that is too small to contain all the required labeling, the agency recommends that the product be enclosed in a carton or be accompanied by a package insert or booklet that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label. Manufacturers who use this supplemental labeling should be able to readily provide all labeling information in a larger print size than if all of the labeling is presented on the immediate container. Further, the agency is aware that many manufacturers use bold lettering and a colored label to emphasize certain labeling information, including warnings, on the immediate container and in package inserts. All manufacturers are encouraged to use these as appropriate to highlight and emphasize certain labeling information for consumers. The agency recently published a request for public comment (56 FR 9363 to 9365, March 6, 1991) on the issue of print size and style of labeling for OTC drug products, and will evaluate comments received before making a final decision on the feasibility of establishing a Federal regulation pertaining to print size and style of OTC labeling. In addition, the Nonprescription Drug Manufacturers Association (NDMA) has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines," NDMA, Washington, copy included in OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.

21. One comment recommended removal of the phrase "difficulty in breathing" from the proposed warning in § 341.72(c)(2), which states "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The comment contended that the phrase "difficulty in breathing" is redundant because the terms asthma, emphysema, chronic pulmonary disease, and shortness of breath specifically describe those breathing problems which may contraindicate antihistamine use. The comment added that the phrase "difficulty in breathing" is too broadly worded and could be interpreted by consumers to mean "difficulty in nasal breathing." The comment argued that such an interpretation could lead to consumer confusion in reading the labeling of an OTC cough-cold combination drug product containing an antihistamine and a nasal decongestant. Such a product would be indicated for relieving nasal congestion but would also state not to use the product if you have difficulty in [nasal] breathing. The comment concluded that removal of the phrase "difficulty in breathing" from the warning would lessen consumer confusion caused by the labeling of some combination products without changing the substance of the warning information provided to consumers.

The agency proposed the warning in § 341.72(c)(2) in the tentative final monograph for OTC antihistamine drug products based on the medical rationale that antihistamines should not be used by patients with any obstructive pulmonary disease in which clearance of secretions is a problem (50 FR 2200 at 2215). In making this proposal, the agency stated that respiratory distress symptoms such as difficulty in breathing and shortness of breath are characteristic of chronic obstructive pulmonary disease. The agency concluded that such descriptive terms should also be included in the warning in addition to the names of the diseases in order to provide more information to the consumer.

The agency disagrees with the comment that the phrase "difficulty in breathing" will be confusing to consumers using single ingredient antihistamine drug products because

such products are not indicated for the relief of nasal congestion. However, the agency does believe that using the broader phrase "breathing problems" to describe such symptoms (e.g., "shortness of breath" and "difficulty in breathing") related to obstructive pulmonary disease would allow the consumer to more readily recognize any respiratory distress symptoms that he/she may experience. Therefore, the agency is deleting the phrases "shortness of breath" and "difficulty in breathing" and replacing them with the phrase "breathing problem" in the warning in § 341.72(c)(2) of this final monograph.

At a meeting on June 11 and 12, 1990, the agency's Pulmonary-Allergy Drugs Advisory Committee discussed the need to continue labeling prescription and OTC antihistamine drug products with a warning against the use of antihistamines by people with asthma (Ref. 1). Participants at the meeting expressed the belief that the warning is no longer accurate, and questioned the continued validity of the reasoning for the warning. It was noted that early first-generation antihistamines, which are no longer on the market, had anticholinergic activity that could be a problem in asthma, but that the newer compounds have been shown to be mildly effective as well as safe in people with asthma. An agency consultant stated that the problem is that many asthmatic patients are also afflicted with upper-airway disorders, and the prescribing physician is on the horns of a dilemma because there is a labeled contraindication about the use of antihistamines by people with asthma, but there is also evidence to show that antihistamines are safe for use by asthmatics. This anomaly places physicians in the awkward position of telling patients to ignore a labeled warning.

The consultant presented a survey of published medical reports and literature to support the position that antihistamines should not be contraindicated in people with asthma unless an individual has previously experienced an adverse reaction (Refs. 2 through 24). Positive effects of antihistamines on asthma have been reported. Investigators have shown that antihistamines may inhibit exercise-induced asthma (Refs. 4, 5, 9 through 12, and 23), and that they may prevent histamine-induced and allergen-induced bronchospasm (Refs. 2, 4, 6, 7, 8, 10, 13, 19, 20, and 23). Further, antihistamines have been demonstrated to be mild bronchodilators that improve pulmonary function (Refs. 4, 5, 10, 19, 23, and 24). A reduction of pulmonary

function has been observed following diphenhydramine, hydroxyzine, and brompheniramine challenges in asthmatic children, but premedication with bronchodilators prevented the decrease (Refs. 14 and 15). Some studies suggest the beneficial effects of antihistamines are dose related (Refs. 4, 5, 9, 12, and 23), while one investigator observed that low concentrations inhibit histamine release, but high concentrations may stimulate histamine release, in vitro, in the absence of antigen challenge (Ref. 12). It is generally believed that histamine released from airway mast cells is a major mediator of bronchospasm, although other mediators may be involved (Refs. 3, 4, 6, 7, 8, 10, 19, 20, 21, 23, and 24). Therefore, as far as the treatment of asthma is concerned, an antihistamine is not the drug of first choice (Refs. 17 and 23), but it need not be withheld from asthmatics who are also afflicted with upper-airway disorders. There does not seem to be any direct evidence that anticholinergic effects of some antihistamines will cause drying of bronchial secretions and exacerbate asthma (Refs. 17 and 23).

The advisory committee was asked to vote on the question of whether current evidence supports continued use of the warning statement about possible adverse effects of antihistamines on asthma. The advisory committee recommended to FDA by a vote of seven to zero, with one abstention, that current evidence does not support continuation of the warning regarding possible adverse effects of antihistamines when used by asthmatic patients and the warning should be rescinded (Ref. 1).

The agency has evaluated the references cited by the consultant (Refs. 2 through 24) and concludes that it concurs with the advisory committee's recommendation. Accordingly, in this final rule, the agency is removing the descriptive term "asthma" from the warning included in § 341.72(c)(2).

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2215), the agency proposed the descriptive term "chronic pulmonary diseases" to cover all types of chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis. However, because consumers may associate the term "chronic pulmonary disease" with asthma, the agency now believes that this term is no longer appropriate and that clarifying the term would be more helpful to consumers. The agency believes that consumers will recognize and understand the terms chronic bronchitis and emphysema and is

replacing the term "chronic pulmonary disease" with "chronic bronchitis" in the warning. The term emphysema already appears in the warning.

With regard to OTC cough-cold combination drug products containing an antihistamine and a nasal decongestant, the agency concurs with the comment that consumers might confuse a phrase describing breathing problems associated with emphysema or chronic bronchitis with those breathing problems associated with nasal congestion when taking an OTC cough-cold combination drug product containing an antihistamine and a nasal decongestant. Thus, to clarify the warning and to avoid any confusion regarding the phrase "breathing problem" for consumers using an OTC cough-cold drug product labeled with antihistamine and nasal decongestant claims, the agency is revising the wording of the warning appearing in § 341.72(c)(2) of this final monograph to associate the breathing problems with the conditions for which an antihistamine should not be used.

Therefore, the agency is revising the warning in § 341.72(c)(2) to reflect the changes discussed above as follows: "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to the enlargement of the prostate gland." The warning has also been revised to group the breathing conditions together in one part of the warning, followed by the other conditions for which the drug should not be used unless directed by a doctor. Likewise, the corresponding warning in § 341.72(c)(6)(i) for products that are labeled only for use by children under 12 years of age is being revised in a similar manner to read: "Do not give this product to children who have a breathing problem such as chronic bronchitis or who have glaucoma, without first consulting the child's doctor." Under proposed § 341.85(c) in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30561), these revised warnings will be applicable to any OTC cough-cold combination drug products containing an antihistamine and a nasal decongestant.

References

- (1) Transcript of the June 12, 1990 meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, pp. 154-172, in OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Hamld, M., P. Rafferty, and S. T. Holgate, "The Inhibitory Effect of Terfenadine and Flurbiprofen on Early and

Late-Phase Bronchoconstriction Following Allergen Challenge in Atopic Asthma," *Clinical and Experimental Allergy*, 20:261-267, 1990.

(3) Flint, K. C., et al., "Bronchoalveolar Mast Cells in Extrinsic Asthma: A Mechanism for the Initiation of Antigen Specific Bronchoconstriction," *British Medical Journal*, 291:923-926, 1985.

(4) Holgate, S. T., and J. P. Finnerty, "Antihistamines in Asthma," *The Journal of Allergy and Clinical Immunology*, 83:537-547, 1989.

(5) Pierson, W. E., et al., "Terfenadine Blockage of Exercise-Induced Bronchospasm," *Annals of Allergy*, 63:461-464, 1989.

(6) Wilmot, C., J. P. Finnerty, and S. T. Holgate, "Role of Histamine and Prostaglandins in the Bronchial Response to Inhaled Hypertonic Saline," *Thorax*, 43:865P, 1988.

(7) Rafferty, P., R. Beasley, and S. T. Holgate, "The Contribution of Histamine to Immediate Bronchoconstriction Provoked by Inhaled Allergen and Adenosine 5' Monophosphate in Atopic Asthma," *American Review of Respiratory Diseases*, 136:369-373, 1987.

(8) Miszkziel, K. A., R. Beasley, and S. T. Holgate, "The Influence of Ipratropium Bromide and Sodium Cromoglycate on Benzalkonium Chloride-Induced Bronchoconstriction in Asthma," *British Journal of Clinical Pharmacology*, 26:295-301, 1988.

(9) Patel, K. R., "Terfenadine in Exercise Induced Asthma," *British Medical Journal*, 288:1496-1497, 1984.

(10) Hartley, J. P. R., and S. G. Nogrady, "Effect of an Inhaled Antihistamine on Exercised-Induced Asthma," *Thorax*, 35:675-679, 1980.

(11) Reinhardt, D., et al., "Effects of the Antiallergic Drug Ketotifen on Bronchial Resistance and Beta-Adrenocaptor Density of Lymphocytes in Children with Exercise-Induced Asthma," *Developmental Pharmacology and Therapeutics*, 11:180-188, 1988.

(12) Silverman, M., and M. Tooley, "Oxatomide and Exercise-Induced Asthma in Children: The Value of Serial Exercise Tests," *Clinical Allergy*, 11:421-428, 1981.

(13) Booij-Noord, H., et al., "Late Bronchial Obstructive Reaction to Experimental Inhalation of House Dust Extract," *Clinical Allergy*, 2:43-61, 1972.

(14) Schuller, D. E., "Adverse Effects of Brompheniramine on Pulmonary Function in a Subset of Asthmatic Children," *The Journal of Allergy and Clinical Immunology*, 72:175-179, 1983.

(15) Schuller, D. E., "The Spectrum of Antihistamines Adversely Affecting Pulmonary Function in Asthmatic Children," *The Journal of Allergy and Clinical Immunology*, 71:147, 1983.

(16) Lavenstein, B. L., and F. K. Cantor, "Acute Dystonia: An Unusual Reaction to Diphenhydramine," *The Journal of the American Medical Association*, 236:291, 1976.

(17) Karlin, J. M., "The Use of Antihistamines in Asthma," *Annals of Allergy*, 30:342-347, 1972.

(18) Simons, F. E. R., et al., "Astemizole-Induced Torsade de Pointes," *The Lancet*, 8611:624, 1988.

(19) Meltzer, E. O., "To Use or Not To Use Antihistamines in Patients with Asthma," *Annals of Allergy*, 64:183-186, 1990.

(20) Rafferty, P., et al., "The Role of Histamine in Allergen and Adenosine-Induced Bronchoconstriction," *International Archives of Allergy and Applied Immunology*, 82:292-294, 1987.

(21) Gravelyn, T. R., P. M. Pan, and W. L. Eschenbacher, "Mediator Release in an Isolated Airway Segment in Subjects with Asthma," *American Review of Respiratory Diseases*, 137:641-646, 1988.

(22) Sly, R. M., et al., "Position Statement: The Use of Antihistamines in Patients with Asthma," *The Journal of Allergy and Clinical Immunology*, 82:481-482, 1988.

(23) Simons, F. E. R., and K. J. Simons, "H1 Receptor Antagonists: Clinical Pharmacology and Use in Allergic Disease," *Pediatric Clinics of North America*, 30:899-914, 1983.

(24) Lewiston, N. J., S. Johnson, and E. Sloan, "Effect of Antihistamine on Pulmonary Function of Children with Asthma," *The Journal of Pediatrics*, 101:458-460, 1982.

22. One comment contended that proposed § 341.72(c)(3) and (4) which presently state "May cause (marked) drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product * * * ." may cause confusion for consumers taking a product formulated with alcohol in that they may interpret the warnings to mean that the products should not be used at all. The comment requested changes in this warning, for products formulated with alcohol and labeled for nighttime use, and suggested the addition of the following as an alternative to § 341.72(c)(3) and (4): "May cause (marked) drowsiness; this product is formulated with alcohol which may increase the drowsiness effect. While taking this product, avoid alcoholic drinks or other products with alcohol."

The agency notes that this comment was submitted before the agency published an amendment to the tentative final monograph for OTC antihistamine drug products in the Federal Register of August 24, 1987. In that amendment, the agency revised the proposed warnings in § 341.72(c)(3) and (4) to read as follows: "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

The intended message of the warnings in § 341.72(c)(3) and (4) is to inform

consumers to avoid alcoholic beverages when using OTC antihistamines because alcoholic beverages may increase the drowsiness effect of the antihistamine. The agency does not believe that a consumer would equate a drug product containing alcohol with an alcoholic beverage and thus construe these warnings to mean that the drug product should not be used. Additionally, the comment did not provide any data supporting its contention that the proposed warning is confusing. Finally, the agency does not believe that products formulated with alcohol and labeled for nighttime use should have a different warning. The agency is aware that such products often are also labeled for use during the day and are, in fact, used by consumers during the day whether or not they contain labeling for this use. The agency believes that products containing an antihistamine should contain the same warnings, with the only exception being that the word "marked" is required for several of the antihistamines to describe the degree of drowsiness that may occur. Therefore, the agency is not including the comment's suggested alternative in § 341.72(c)(3) and (4) of this final monograph, but is including the warning that was proposed in the amendment to the tentative final monograph for OTC antihistamine drug products, as stated above.

23. One comment suggested that labeling for drug products containing diphenhydramine, chlorpheniramine, and related substances should contain warnings of possible effects on the heart, particularly heart problems requiring treatment with beta blocker drugs. The comment based its suggestion on a personal experience while using a prescription drug product containing diphenhydramine "for a bad case of allergy" and, subsequently, using an OTC drug product containing chlorpheniramine. The comment contended that these drugs "began to cause trouble, a stepped-up heart beat, and a very disabling weak feeling in the chest."

The agency has reviewed the Panel's report with respect to side effects of the antihistamines. The Panel stated that the most common side effects are drowsiness and dryness of the mouth (41 FR 38312 at 38380). The Panel also stated that other side effects which are not as common have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects and cardiovascular symptoms which may include palpitations, hypotension, headache, or tightness of the chest (41

FR 38380). The Panel concluded that serious side effects produced by the antihistaminic drugs in the dosages recommended for OTC use are rare and the more common side effects are rarely serious (41 FR 38380). In addition, in its safety discussions of diphenhydramine (41 FR 38340, 38341, 38384, and 38385), chlorpheniramine (41 FR 38383 and 38384), or any other Category I antihistamine, the Panel did not cite any cardiovascular problems associated with the use of these ingredients as mentioned specifically by the comment. The comment did not submit any data to support its suggestion to add warnings concerning cardiovascular effects to the labeling of OTC antihistamine drug products beyond reporting one personal experience.

Based on the Panel's determination that cardiovascular symptoms rarely occur with the use of OTC antihistamines, and the lack of other information, the agency concludes that there is not an adequate basis for OTC antihistamine drug products to bear label warnings regarding possible adverse cardiovascular effects. Accordingly, the agency is not including such warnings in this final monograph.

24. One comment suggested that all antihistamine drug products contain warnings to the elderly that these products may produce congestion in the lungs, particularly in case of bronchitis, flu, pneumonia, or even a bad cold.

The comment did not provide any data demonstrating that lung congestion results from taking an OTC antihistamine drug product. The agency is not aware of any studies or published literature that would support the comment's statement. If lung congestion occurs when a person has bronchitis, flu, pneumonia, or a bad cold, it would appear that the congestion is likely the result of the underlying condition. The agency does not believe that a warning expanded beyond that discussed in comment 21, "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland," is warranted at this time.

25. Two comments requested that the agency include the symptomatic treatment of allergic itching as a monograph condition in the final monograph for OTC antihistamine drug products. One comment requested this indication specifically for oral diphenhydramine, while the other comment requested the indication for all orally administered OTC antihistamines.

The comment that requested monograph status for oral diphenhydramine requested the following indication: "For temporary relief of itching associated with hives, minor skin irritations, or rashes due to food or animal allergies, insect bites, inhaled allergens (dust, mold, spores), poison ivy, oak, or sumac, soaps, detergents, cosmetics, and jewelry." The comment contended that the proposed indication involves only symptoms which consumers can recognize and treat, and that the indication is currently approved for prescription dispensing of diphenhydramine hydrochloride at the dose already accepted for OTC marketing. This comment was subsequently withdrawn, but no reasons were given (Ref. 1).

The second comment cited statements from three references to support the effectiveness of orally administered antihistamines for the relief of pruritus, angioedema, and other manifestations of skin allergies: (1) prior administration of chlorpheniramine raised the itch thresholds to both 2-methyl histamine and histamine itself (Ref. 2), (2) traditional antihistamines of the H1 type are the mainstay in the management of urticaria (Ref. 3), and (3) certain of the allergic dermatoses respond favorably to H1 blockers; H1 blockers also have a place in the treatment of itching pruritides; and some relief may be obtained in many patients suffering atopic dermatitis and contact dermatitis, although topical corticosteroids seem to be more valuable in such diverse conditions as insect bites and ivy poisonings (Ref. 4). The comment requested that the indications in § 341.72(b) be expanded to permit the following claim: " * * * or the itching skin caused by allergy to local irritants such as poison ivy, oak, or sumac, or caused by hives."

The agency has reviewed the information provided by the comment and determined that it is insufficient to support general recognition of the symptomatic treatment of allergic itching as an appropriate OTC indication for oral antihistamine drug products. Hives and pruritic rashes secondary to foods, animal allergies, and insect stings and bites can be one component of a systemic anaphylactic reaction, and the use of an OTC antihistamine could potentially delay more appropriate treatment that may be needed. The agency is unaware of any data demonstrating that the average person can distinguish between a mild allergic reaction and a life-threatening reaction that may begin with itching only. Histamine is only one of the mediators released during mast cell

degranulation (Ref. 5). Therefore, the use of an antihistamine alone may not be sufficient.

The agency does not find that the references cited by the comment support OTC use of oral antihistamines for pruritus, angioedema, and other manifestations of skin allergies. For example, Monroe (Ref. 3) also said that the ideal treatment for urticaria is identification and removal of its cause and that oral antihistamines of the H1 type are the usual medical treatment for acute urticaria, but medical management is required in severe urticarial reactions. Further, the edition of Goodman and Gilman cited by the comment included in its discussion of allergic dermatoses the caveat that, although angioedema is responsive to treatment with antihistamines, the paramount importance of epinephrine in the severe attack must be emphasized (Ref. 4). This caution is carried through to the current edition of Goodman and Gilman as well (Ref. 5). Poison ivy, oak, and sumac are examples of contact dermatitis. The Merck Manual (Ref. 6) states that, although an oral corticosteroid should be given in severe cases and the treatment for contact dermatitis is usually topical corticosteroids, antihistamines are ineffective in cases of contact dermatitis except for their sedative effect.

Based upon currently available data, the agency concludes that there is a lack of information to support an OTC indication for allergic itching related to hives and rashes. Thus, the use of OTC oral antihistamines for self-treatment of these problems remains a nonmonograph condition at this time.

References

- (1) Comment No. WDL 1, Docket No. 76N-052H, Dockets Management Branch.
- (2) Davies, M. C., and M. W. Greaves, "The Current Status of Histamine Receptors in Human Skin: Therapeutic Implications," *British Journal of Dermatology*, 104:601-606, 1981.
- (3) Monroe, E. W., "Treatment of Urticaria," *Dermatologic Clinics*, 3:51-55, 1985.
- (4) Douglas, W. W., "Histamine and 5-Hydroxytryptamine (Serotonin) and Their Antagonists," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 6th Ed., edited by A. G. Gilman, L. S. Goodman, and A. Gilman, Macmillan Publishing Co., New York, pp 622-646, 1980.
- (5) Garrison, J. C., and T. W. Rall, "Histamine, Bradykinin, 5-Hydroxytryptamine, and Their Antagonists," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 8th Ed., edited by A. G. Gilman, et al., Pergamon Press, New York, pp. 574-588.
- (6) Berkow, R., editor, "The Merck Manual," 15th Ed., Merck & Co., Inc., Rahway, NJ, pp. 2255-2257, 1987.

II. Summary of Significant Changes From the Proposed Rule

1. The agency has determined that diphenhydramine citrate should be included in this final monograph because the citrate salt of diphenhydramine is identical to the hydrochloride salt. A dose of 76 mg diphenhydramine citrate supplies an equivalent amount of diphenhydramine hydrochloride. Therefore, the agency is revising the letter designations of active ingredients in § 341.12 *Antihistamine active ingredients* to include the addition of diphenhydramine citrate in this section. The agency is also revising and redesignating the paragraphs in §§ 341.72 (c) and (d) and 341.90 to reflect this addition to § 341.12. (See comment 4.)

2. In order to allow for greater flexibility in indication statements, the agency is revising and expanding § 341.72(b) to allow for the option of using either the phrase "Temporarily relieves" or "For the temporary relief of." This revision results in the addition of a new indication in § 341.72(b)(2); proposed § 341.72(b)(2) (indication for a cold) is temporarily removed while the agency further assesses the use of antihistamines for relieving symptoms of a cold. New § 341.72(b)(2) now reads as follows: "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)"). (See comment 14.)

3. The agency is clarifying and revising the warning in § 341.72(c)(2) so that the consumer will not confuse "breathing problems" associated with nasal congestion with "breathing problems" associated with emphysema or chronic bronchitis (conditions for which an antihistamine should not be used) when taking an OTC cough-cold combination drug product containing an antihistamine and a nasal decongestant and to delete the term "asthma." The agency is revising the warning to read as follows: "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland." Likewise, the corresponding warning in § 341.72(c)(6)(i) for products that are labeled only for use by children under 12 years of age is also revised to read as follows: "Do not give this product to children who have a breathing problem such as chronic bronchitis or who have

glaucoma, without first consulting the child's doctor." (See comment 21.)

4. The agency is deferring its final decision on the monograph status of doxylamine succinate. Thus, the agency has deleted this ingredient from § 341.12 of the monograph, all references to this ingredient from headings in the monograph, and the directions for the use of this ingredient from § 341.72(d) and 341.90.

5. The agency is revising the letter designations proposed on January 15, 1985, and August 24, 1987, in the following sections: in § 341.3 *Definitions*, (d) is being redesignated as (e); and in § 341.90 *Professional Labeling*, paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), and (m) have been redesignated as paragraphs (e), (f), (g), (h), (i), (k), (l), (m), (n), (o), (p), and (q), respectively. The redesignated paragraph "1" is being reserved because the agency is deferring its final decision on the status of doxylamine succinate. Also, new paragraph (j) for the ingredient diphenhydramine citrate is being added to § 341.90.

6. The agency is deferring its final decision on the OTC claim for the common cold proposed in § 341.72(b) of the tentative final monograph until the scientific debate about such use is resolved as discussed above. Thus, the agency is deleting the portion of the definition proposed in § 341.3(e) that refers to the common cold and the indication proposed in § 341.72(b) for the use of OTC antihistamines for symptoms of the common cold.

III. The Agency's Final Conclusions on OTC Antihistamine Drug Products for Relief of Symptoms of Hay Fever and Upper Respiratory Allergies (Allergic Rhinitis)

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antihistamine drug products are generally recognized as safe and effective and not misbranded for relief of symptoms of hay fever and upper respiratory allergies (allergic rhinitis). Specifically, the following ingredients are included in this final monograph for OTC antihistamine use:

- brompheniramine maleate,
- chlorcyclizine hydrochloride,
- chlorpheniramine maleate,
- dexbrompheniramine maleate,
- dexchlorpheniramine maleate,
- diphenhydramine citrate,
- diphenhydramine hydrochloride,
- phenindamine tartrate,
- pheniramine maleate,
- pyrilamine maleate,
- thonzylamine hydrochloride,
- triprolidine hydrochloride.

The following ingredients for OTC

antihistamine use considered in this rulemaking are nonmonograph ingredients: methapyrilene fumarate, methapyrilene hydrochloride, phenyltoloxamine dihydrogen citrate, promethazine hydrochloride, thenyldiamine hydrochloride, and tripeleminamine hydrochloride. The agency has established 21 CFR 310.545 in which it lists certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. Methapyrilene hydrochloride, methapyrilene fumarate, and thenyldiamine hydrochloride are presently listed in § 310.545(a)(6)(i) for antihistamine drug products. In this final rule, the agency is amending § 310.545(a)(6)(i) by adding phenyltoloxamine dihydrogen citrate, Promethazine hydrochloride (as a single ingredient) and tripeleminamine hydrochloride are not included in § 310.545 because these ingredients have not been marketed OTC and were considered in this rulemaking only as possible prescription-to-OTC switch drugs. Promethazine hydrochloride in cough-cold combination drug products will be discussed in the final rule for OTC cough-cold combination drug products in a future issue of the Federal Register. The use of antihistamines to relieve symptoms of a cold will be discussed in a future issue of the Federal Register.

Any drug product marketed for use as an OTC antihistamine drug product that is not in conformance with the monograph (21 CFR part 341, subparts A, B, and C) (except the labeling of an antihistamine included in the monograph to relieve symptoms of a cold) is considered misbranded under section 502 of the act (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application or abbreviated 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 amend the monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any OTC antihistamine 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 regulations is subject to regulatory action. The effective date of this final monograph does not apply to antihistamines marketed for relief of symptoms of a cold. Such products may remain in the marketplace while the agency continues its review of antihistamines for this use.

However, any product containing an antihistamine and labeled for use to relieve both symptoms of hay fever and a cold must bear all of the required monograph labeling on or before the effective date of this final rule. Manufacturers of products containing an antihistamine labeled only to relieve symptoms of a cold are encouraged to voluntarily label the product with all of the information required by this final monograph. However, such products may not bear the FDA "APPROVED USES" language provided for in § 330.1(c)(2)(i).

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2200, at 2215 through 2216 and 52 FR 31892 at 31911). 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 antihistamine 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 antihistamine drug products is not expected to pose such an impact on small businesses. This final rule will require some relabeling for products containing monograph ingredients. Manufacturers will have one year to implement this relabeling. This final rule does not affect antihistamine products labeled to relieve symptoms of a cold. This final rule will also require reformulation of a few products containing phenyltoloxamine dihydrogen citrate. For all other nonmonograph active ingredients listed above, the effective date was May 7, 1991. Therefore, the agency certifies that this final rule will not have a significant economic impact

on a substantial number of small entities.

The agency is removing § 201.307 and removing the exemption for certain drugs limited by NDA's to prescription sale in § 310.201(a)(25) (applicable to chlorcyclizine hydrochloride preparations) because most portions of those regulations are superseded by the requirements of the antiemetic final monograph (21 CFR part 336) and the antihistamine final monograph (21 CFR part 341) (for chlorcyclizine hydrochloride). Section 201.307 also addresses the marketing of parenteral drugs containing chlorcyclizine, cyclizine, or meclizine. These products are all marketed as prescription drugs and, as such, must comply with the pregnancy labeling requirements of § 201.57 (21 CFR 201.57). Accordingly, § 201.307 is no longer required. The agency is also adding and reserving paragraph (b) in § 310.201, and amending an entry in §§ 369.20 and 369.21. The items being removed include: (1) all of § 201.307; (2) § 310.201(a)(25); and (3) the references to § 201.307 and § 310.201(a)(25) in the introductory text of the entry for "ANTIHISTAMINICS, ORAL" in § 369.20. The agency is also removing the reference to paragraph (a)(6) of § 310.201 in this same entry because that paragraph was removed on April 30, 1987 and reserved for future use. (See 52 FR 15886 at 15892.) In this final rule, the agency is amending § 310.545 by adding phenyltoloxamine dihydrogen citrate in paragraph (a)(6)(i), and by adding new paragraph (d)(6). The agency is also revising the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS)" in § 369.21 by revising the introductory text and by removing those portions of the entry pertaining specifically to chlorcyclizine hydrochloride, including the references to § 201.307 and paragraphs (a)(6) and (a)(25) of § 310.201 in this entry.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 310

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

21 CFR Part 341

Antihistamine drug products, Labeling, Over-the-counter drugs.

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, 21 CFR parts 201, 310, 341, and 369 are 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, 706 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, 376); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

§ 201.307 [Removed]

2. Section 201.307 *Chlorcyclizine, cyclizine, meclizine; warnings; labeling requirements* is removed from subpart G.

PART 310—NEW DRUGS

3. 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).

§ 310.201 [Amended]

4. Section 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(25) and reserving it, and by adding and reserving paragraph (b).

5. Section 310.545 is amended by revising paragraph (a)(6)(i), paragraphs (d) introductory text and (d)(1), and by adding new paragraph (d)(6) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

- (a) * * *
- (6) * * *

(i) *Antihistamine drug products.* (A) *Ingredients.*
Methapyrilene hydrochloride
Methapyrilene fumarate
Thenylamine hydrochloride

(B) *Ingredient.*

Phenyltoloxamine dihydrogen citrate

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(6) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(6)(i)(A), (a)(6)(ii), (a)(7) (except as covered by paragraph (d)(3) of this section) through (a)(19) of this section.

(6) December 9, 1993, for products subject to paragraph (a)(6)(i)(B) of this section.

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

6. 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).

7. Section 341.3 is amended by adding new paragraph (e) to read as follows:

§ 341.3 Definitions.

(e) *Antihistamine drug.* A drug used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis).

8. Section 341.12 is added to subpart B to read as follows:

§ 341.12 Antihistamine active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient:

- (a) Brompheniramine maleate.
- (b) Chlorcyclizine hydrochloride.
- (c) Chlorpheniramine maleate.
- (d) Dexbrompheniramine maleate.
- (e) Dexchlorpheniramine maleate.
- (f) Diphenhydramine citrate.
- (g) Diphenhydramine hydrochloride.
- (h) [Reserved]
- (i) Phenindamine tartrate.
- (j) Pheniramine maleate.
- (k) Pyrilamine maleate.
- (l) Thonzylamine hydrochloride.
- (m) Triprolidine hydrochloride.

9. Section 341.72 is added to subpart C to read as follows:

§ 341.72 Labeling of antihistamine drug products.

(a) *Statement of identity.* The labeling of the product contains the established

name of the drug, if any, and identifies the product as an "antihistamine."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(2) "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children."

(2) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland."

(3) *For products containing brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (e), (i), (j), (k), (l), and (m).* "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor

Use caution when driving a motor vehicle or operating machinery."

(4) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(5) *For products containing phenindamine tartrate identified in § 341.12(i).* "May cause nervousness and insomnia in some individuals."

(6) *For products that are labeled only for use by children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c)(1) and (c)(5) of this section as well as the following:

(i) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (c), (d), (e), (i), (j), (k), (l), and (m).* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iii) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride or identified in § 341.12(f) and (g).* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing brompheniramine maleate identified in § 341.12(a).* Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2

milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(2) *For products containing chlorcyclizine hydrochloride identified in § 341.12(b).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 12 years of age: consult a doctor.

(3) *For products containing chlorpheniramine maleate identified in § 341.12(c).* Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) *For products containing dexbrompheniramine maleate identified in § 341.12(d).* Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) *For products containing dexchlorpheniramine maleate identified in § 341.12(e).* Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) *For products containing diphenhydramine citrate identified in § 341.12(f).* Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) *For products containing diphenhydramine hydrochloride identified in § 341.12(g).* Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4

to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) [Reserved]

(9) *For products containing phenindamine tartrate identified in § 341.12(i).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) *For products containing pheniramine maleate identified in § 341.12(j).* Adults and children 12 years of age and over: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(11) *For products containing pyrilamine maleate identified in § 341.12(k).* Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(12) *For products containing thonzylamine hydrochloride identified in § 341.12(l).* Adults and children 12 years of age and over: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(13) *For products containing triprolidine hydrochloride identified in § 341.12(m).* Adults and children 12 years of age and over: oral dosage is 2.5 milligrams every 4 to 6 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 4 to 6 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any

of the labeling statements in this section.

10. Section 341.90 is amended by adding paragraphs (e) through (q) to read as follows:

§ 341.90 Professional labeling.

(e) For products containing brompheniramine maleate identified in § 341.12(a). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(f) For products containing chlorcyclizine hydrochloride identified in § 341.12(b). Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

(g) For products containing chlorpheniramine maleate identified in § 341.12(c). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(h) For products containing dexbrompheniramine maleate identified in § 341.12(d). Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(i) For products containing dexchlorpheniramine maleate identified in § 341.12(e). Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(j) For products containing diphenhydramine citrate identified in § 341.12(f). Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

(k) For products containing diphenhydramine hydrochloride identified in § 341.12(g). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(l) [Reserved]

(m) For products containing phenindamine tartrate identified in § 341.12(i). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(n) For products containing pheniramine maleate identified in § 341.12(j). Children 2 to under 6 years of age: oral dosage is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(o) For products containing pyrrolamine maleate identified in § 341.12(k). Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(p) For products containing thonzylamine hydrochloride identified in § 341.12(l). Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(q) For products containing triprolidine hydrochloride identified in § 341.12(m). Children 4 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 4 to 6 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

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

11. 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]

13. Section 369.20 *Drugs; recommended warning and caution*

statements is amended by revising the introductory text of the entry for "ANTIHISTAMINICS, ORAL" to read: "ANTIHISTAMINICS, ORAL. (See also § 310.201(a)(4) and (a)(24) of this chapter.)"

§ 369.21 [Amended]

13. Section 369.21 *Drugs; warning and caution statements required by regulations* is amended by revising the introductory text of the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS)" to read: "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, AND CHLOROTHEN CITRATE PREPARATIONS). (See § 310.201(a)(4), (a)(13), and (a)(24) of this chapter.)" and by removing the warning statement for chlorcyclizine-containing preparations.

Dated: August 5, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 92-29718 Filed 12-8-92, 8:45 am]

BILLING CODE 4160-01-F

Foreign Countries with Prescription-Free Marketing of Loratadine

Country	Marketing Class	Prescription-Free Date ¹	Labeling Statements Referencing CIU ^{2,3}
Australia	Pharmacy	1994	<ul style="list-style-type: none"> • "... relief from the symptoms of ... and chronic urticaria (hives) ..." • "... provides relief from ... itchy rash"
Austria	Pharmacy	1996	<ul style="list-style-type: none"> • "... alleviation of the unpleasant secondary symptoms ... and in cases of chronic hives (itching and redness of skin)."
Azerbaijan	Pharmacy	1996	not available
Belgium	OTC	1991	<ul style="list-style-type: none"> • "... alleviation of the symptoms that are caused by a rash, such as itching, redness and skin rash."
Canada	OTC	1990	see Attachment 4
Denmark	Pharmacy	1990	<ul style="list-style-type: none"> • "... urticaria ... and symptoms similar to allergies"
Finland ⁴	n/a	n/a	not available
Georgia	Pharmacy	1996	not available
Germany	OTC	1994	<ul style="list-style-type: none"> • "For the symptomatic treatment of chronic urticaria (hives) with itching, redness and welts on skin as symptoms"
Hong Kong	Pharmacy	1988	<ul style="list-style-type: none"> • "... relief of symptom and signs of chronic urticaria and other allergic dermatologic disorders."
Iceland	Pharmacy	1993	not available

Labeling Statements Referencing CIU ^{2,3}			
Country	Marketing Class	Prescription-Free Date ¹	
Ireland	OTC	1992	<ul style="list-style-type: none"> • "... for allergic skin conditions such as rash, itching or urticaria (hives)."
Israel	Pharmacy	1990	not available
Jordan	Pharmacy		<ul style="list-style-type: none"> • "... relief of symptom and signs of chronic urticaria and other allergic dermatologic disorders."
Kazakhstan	Pharmacy	1993	not available
Luxembourg	Pharmacy	1993	not available
Malaysia	Pharmacy	1989	<ul style="list-style-type: none"> • "... relief of symptom and signs of chronic urticaria and other allergic dermatologic disorders." • "... relief from: allergic rhinitis, skin allergy"
Mexico	Pharmacy	1988	not available
Netherlands	OTC	1990	<ul style="list-style-type: none"> • "... alleviating symptoms, such as itching, redness and skin rash." • "... combating the phenomena of a long-term rash, such as severe itching and formation of wheals."
New Zealand	Pharmacy	1988	<ul style="list-style-type: none"> • "... relief of symptoms and signs of chronic urticaria (hives) and other allergic skin disorders." • "... relieve conditions associated with a skin condition called urticaria (also called hives); these symptoms include itching, redness and lumps on the skin."
Norway	Pharmacy	1994	not available
Philippines ⁴	n/a	n/a	not available
Poland ⁴	n/a	n/a	not available

Country	Marketing Class	Prescription-Free Date ¹	Labeling Statements Referencing CIU ^{2,3}
Russia	OTC	1992	not available
Singapore	Pharmacy	1989	not available
Slovenia	Pharmacy	1994	• "... prevention & cure . . . of chronic urticaria and other allergic skin diseases"
South Africa	Pharmacy	1990	• "... relief of symptom and signs of chronic urticaria and other allergic dermatologic disorders."
Sweden ⁴	n/a	n/a	• "Other areas of application, follow physician's instructions"
Switzerland	Pharmacy	1997	• "... preventive and symptomatic treatment of . . . as well as chronic hives (urticaria)"
Thailand	Pharmacy	1990	• "Relief of symptoms associated with allergic condition of nasal mucosa and skin." • "... for allergic dermatitis, urticaria . . ."
Trinidad	Pharmacy	1990	not available
Ukraine	Pharmacy	1999	not available
UK	OTC	2001	see Attachment 5

¹Prescription-free date refers to 10 mg tablet with CIU indication; earliest date listed for multiple drug products.

²Multiple labeling statements represent labeling on PDP and insert on single product or labeling for multiple products.

³Hong Kong, Jordan, Malaysia, and South Africa have identical labeling.

⁴Country does not allow a prescription-free CIU indication.

Canada

CLARITIN est un antihistaminique qui agit vite et pendant longtemps. Il permet de soulager le rhume des foins et d'enrayer éternuements, écoulement nasal et larmoiement, sans provoquer de somnolence.

MISE EN GARDE: Les femmes enceintes ou allaitantes et les personnes souffrant de maladies du foie doivent consulter un médecin avant de prendre ce produit. Monographie fournie sur demande aux professionnels de la santé. Conserver ce produit et tout autre médicament en lieu sûr, hors de la portée des enfants. Conserver entre 2° et 30 °C.

POSOLOGIE: Adultes et enfants de plus de 10 ans (poids corporel de plus de 30 kg): 10 mL (2 c. à thé) de sirop CLARITIN une fois par jour. Enfants de 2 à 9 ans (poids corporel de 30 kg ou moins): 5 mL (1 c. à thé) de sirop CLARITIN une fois par jour. Ne jamais dépasser la posologie recommandée. Ne jamais prolonger l'emploi, ni utiliser chez des enfants de 2 à 12 ans pendant plus de 14 jours consécutifs, sans l'avis du médecin. N'est pas recommandé pour les enfants de moins de 2 ans.

COMPOSITION: Chaque mL de sirop contient 1 mg de loratadine dans un excipient de propylène glycol, de glycérine, d'acide citrique monohydraté, de benzoate de sodium, de sucre, d'arôme de pêche artificiel et d'eau purifiée.



7-123812

loratadine 1 mg/mL
CLARITIN
Allergy

NON-DROWSY

SYRUP
100 mL

24-HOUR
RELIEF



0 56219 94 100 9



586

United Kingdom



CLARITYN[®] Allergy tablets

Each tablet contains loratadine 10 mg.

CLARITYN Allergy can relieve allergic symptoms due to hayfever and other allergic allergies such as house dust mite and pet allergies. CLARITYN Allergy may also be taken for allergic skin conditions including rash, itching and urticaria (hives).

One tablet starts to work within minutes and delivers a full 24 hours relief - without making you drowsy.

Dosage: Adults and children over 12 years: Swallow one tablet once daily at the first sign of allergic symptoms.

Warning: Do not exceed the stated dose.

Do not use during pregnancy, or if you are breast feeding. If symptoms persist consult your doctor or pharmacist. Keep all medicines out of the reach of children. Also contains hydroxy benzoyl, maize starch and magnesium stearate. PL 02010/175

For hayfever and other allergies

7 tablets

EXP. DATE

LOT NO.

CLARITYN[®] Allergy Leaflet enclosed

061103383CA
MBC2

CLARITYN[®] Allergy

CLARITYN[®]

Loratadine

Allergy tablets

For hayfever and other allergies

Fast acting

No drowsiness 24hr relief

CLARITYN[®] Allergy

5 012376 022192

MBC2 (34707)

United Kingdom

CLARITYN[®] Allergy tablets

Loratadine

06UU23705IN

Patient Information Leaflet

Please read this leaflet carefully

This leaflet will tell you about *Clarityn Allergy* tablets. It should give you all the information you need, but if there is anything you do not understand please ask your doctor or your pharmacist.

What is in *Clarityn Allergy* tablets?

Each tablet contains 10mg of loratadine as the active ingredient as well as the following inactive ingredients:

- Hydrous lactose
 - Maize starch
 - Magnesium stearate.
- There are 7 tablets in this pack.

What is the type of medicine in *Clarityn Allergy* tablets?

The medicine contained in *Clarityn Allergy* tablets is a non-sedating antihistamine. It can help relieve the symptoms of some allergies.

Who makes it?

The product licence holder is:
Schering-Plough Ltd., Shire Park, Welwyn Garden City, Herts AL7 1TW.

The manufacturer is:
Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium.

What are *Clarityn Allergy* tablets for?

In adults, *Clarityn Allergy* tablets can rapidly relieve allergy symptoms such as sneezing, runny nose and itchy, burning eyes, whether these are due to hayfever or whether they occur all year round. *Clarityn Allergy* tablets may also be taken for allergic skin conditions such as rash, itching or urticaria (hives).

Is there any reason why you shouldn't take *Clarityn Allergy* tablets?

If you have ever had an allergic reaction to *Clarityn Allergy* tablets or any of the active or inactive ingredients you should not take them.

You should not take them if you are pregnant or think that you are pregnant or if you are breast-feeding.

Before taking *Clarityn Allergy* tablets

There have been no reports of undesirable effects occurring when *Clarityn Allergy* tablets have been taken at the same time as some other medicines. However, before you start taking *Clarityn Allergy* tablets, you should still tell your doctor or pharmacist if you are taking medicine for any other illness or condition.

You do not have to avoid drinking alcohol whilst taking *Clarityn Allergy* tablets.

Driving and *Clarityn Allergy* tablets

Tests have shown that *Clarityn Allergy* tablets do not cause drowsiness, so you can still drive whilst you are taking your tablets.

What is the dose?

Adults and children aged 12 years and over:
One tablet to be swallowed once daily.

United Kingdom

What to do if you forget to take your medicine

If you forget to take it, take your recommended dose as soon as you remember.

What you should do in the case of an overdose

If you, (or someone else) accidentally takes too many *Claritin Allergy* tablets by mistake, you should contact your doctor immediately.

Meanwhile, try to make yourself (or the other person) vomit. Do not try to do this if you or the other person are not fully awake.

Do *Claritin Allergy* tablets have any undesirable effects?

Most people do not have any side effects after taking *Claritin Allergy* tablets, but as with all medicines, it may not suit everyone. The following side effects have occurred, but only rarely: Tiredness, nausea, headache, hair loss, allergic shock, effects on the liver and disturbances in heart rhythm. Also, a fast heart beat and fainting have been very rarely reported in a few people, although these may not necessarily have been caused by *Claritin Allergy* tablets.

If you are worried by these or any other side effects, you should discuss them with your doctor or pharmacist.

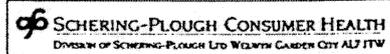
Expiry date

Do not use after the date which is stamped on the pack.

Any other questions?

If there is anything about *Claritin Allergy* tablets you do not understand or are unsure about, your doctor or pharmacist will be able to help or advise you.

Date of revision: October 2000.



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26J022705PMS

PRESSPHARMA PM2 IN39V (130 x 205 mm) 06UU23705IN (recto) pms 280 blue

United Kingdom

Contents: 100 ml plastic
 bottle with
 black plastic
 cap



CLARITYN
Loratadine
Allergy syrup

<p>CLARITYN[®] Allergy syrup Loratadine</p> <p>Fast relief from the symptoms of hayfever and allergic rhinitis e.g. sneezing, itchy and runny nose, congestion, itchy eyes, and from the symptoms of some skin allergies e.g. urticaria (hives).</p>	<p>CLARITYN[®] Allergy syrup Loratadine</p> <p>For hayfever and other allergies</p> <p>Fast acting No drowsiness 24hr relief</p> <p>60ml e</p>	<p>CLARITYN[®] Allergy syrup Loratadine</p> <p>Each 5ml contains 5mg Loratadine, Preservative Sodium Benzoate 0.1% w/v (E211). Contains sucrose. See leaflet for details.</p> <p>Directions for use: Adults and children over 6 years: two 5ml spoons once daily. Children 2-6 years: one 5ml spoon once daily.</p> <p>Warning: Do not exceed the stated dose.</p> <p>Do not use during pregnancy. If symptoms persist consult your doctor.</p> <p>KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN</p> <p>PL 0201/0173</p> <p>Store between 2° and 30°C in the original container.</p>	<p>CLARITYN[®] Allergy syrup Loratadine</p> <p>For hayfever and other allergies</p> <p>Fast acting No drowsiness 24hr relief</p> <p>60ml e</p>
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5 012376 027371

05UU23667CA
BC8

B.N.
Use by



PM2 06UU23667CA

pms 362 green

pms 280 blue pms Clarityn Cyan black

United Kingdom

CLARITYN[®] Allergy syrup

Loratadine

DEL207114

PATIENT INFORMATION LEAFLET

Please read this leaflet carefully

This leaflet will tell you about *Clarityn Allergy* syrup. It should give you all the information you need, but if there is anything you do not understand please ask your doctor or your pharmacist.

What is in *Clarityn Allergy* syrup?

The syrup contains 5mg of the active ingredient, loratadine in each 5ml (about one teaspoonful) as well as the following inactive ingredients: Propylene glycol, glycerine, sucrose (granulated), citric acid, sodium benzoate (E211), peach flavouring. Each bottle contains 60ml syrup

What type of medicine is *Clarityn Allergy* syrup?

Clarityn Allergy syrup is a non-sedating antihistamine. It can help relieve the symptoms of some allergies.

Who makes it?

The product licence holder is
Schering-Plough Ltd., Shire Park, Welwyn Garden City, Hertfordshire AL7 1TW.

The manufacturer is
Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium.

What is *Clarityn Allergy* syrup for?

In adults, *Clarityn Allergy* syrup can rapidly relieve allergy symptoms such as sneezing, runny nose and itchy, burning eyes, whether these are due to hayfever or whether they occur all year round.

Clarityn Allergy syrup may also be taken for allergic skin conditions such as rash, itching or urticaria (hives)

In children (aged 2-12 years) *Clarityn Allergy* syrup may be given for symptoms of hayfever or allergic skin conditions

Is there any reason why you shouldn't take *Clarityn Allergy* syrup?

If you have ever had an allergic reaction to *Clarityn Allergy* syrup or any of its active or inactive ingredients you should not take it

You should not take it if you are pregnant or think that you are pregnant or if you are breast-feeding.

Children aged under 2 years should not take *Clarityn Allergy* syrup.

Antihistamines may prevent response to allergens in skin allergy testing; therefore *Clarityn Allergy* syrup should be stopped four days before any such testing.

Before taking *Clarityn Allergy* syrup

There have been no reports of undesirable effects occurring when *Clarityn Allergy* syrup has been taken at the same time as some other medicines.

However, before you start taking *Clarityn Allergy* syrup, you should still tell your doctor or pharmacist if you are taking medicine for any other illness or condition.



United Kingdom

For example, cimetidine (for the treatment of indigestion and stomach ulcers); erythromycin (an antibiotic); ketoconazole or fluconazole (antifungals); quinidine (for heart problems) or fluoxetine (for treating depression).

Each 5ml dose of *Claritin Allergy* syrup contains 3g of sucrose which may result in a maximum daily intake of 6g of sucrose.

The syrup form of *Claritin* is therefore not suitable for people who suffer from an inherited fruit sugar intolerance, or who are unable to absorb or breakdown sugars in the body.

Driving and *Claritin Allergy* syrup

Studies have shown that *Claritin Allergy* syrup does not cause any more drowsiness than placebo. It does not affect your performance and so will not normally affect your ability to drive or perform tasks requiring concentration.

What is the dose?

Adults and children over 6 years:
Two 5ml spoons once daily.

Children 2-5 years:
One 5ml spoon once daily.

What to do if you forget to take your medicine

If you forget to take your syrup, take your recommended dose as soon as you remember, and then carry on as before.

What you should do in the case of an overdose

If you, (or someone else) accidentally takes too much *Claritin Allergy* syrup by mistake, you should contact your doctor immediately. Meanwhile, try to make yourself (or the other person) vomit. Do not try to do this if you or the other person are not fully awake.

Does *Claritin Allergy* syrup have any undesirable effects?

Most people do not have any side effects after taking *Claritin Allergy* syrup, but as with all medicines, it may not suit everyone. The following side effects have occurred, but only rarely: tiredness, nausea, headache, hair loss, allergic shock, effects on the liver and disturbances in heart rhythm. Also, a fast heart beat and fainting have been very rarely reported in a few people, although these may not necessarily have been caused by *Claritin Allergy* syrup.

If you are worried by these or any other side effects, you should discuss them with your doctor or pharmacist.

Expiry date

Do not use after the date which is stamped on the pack.

Storage information

This medicine should be stored at a temperature of between 2 and 30°C in the original container.

Any other questions?

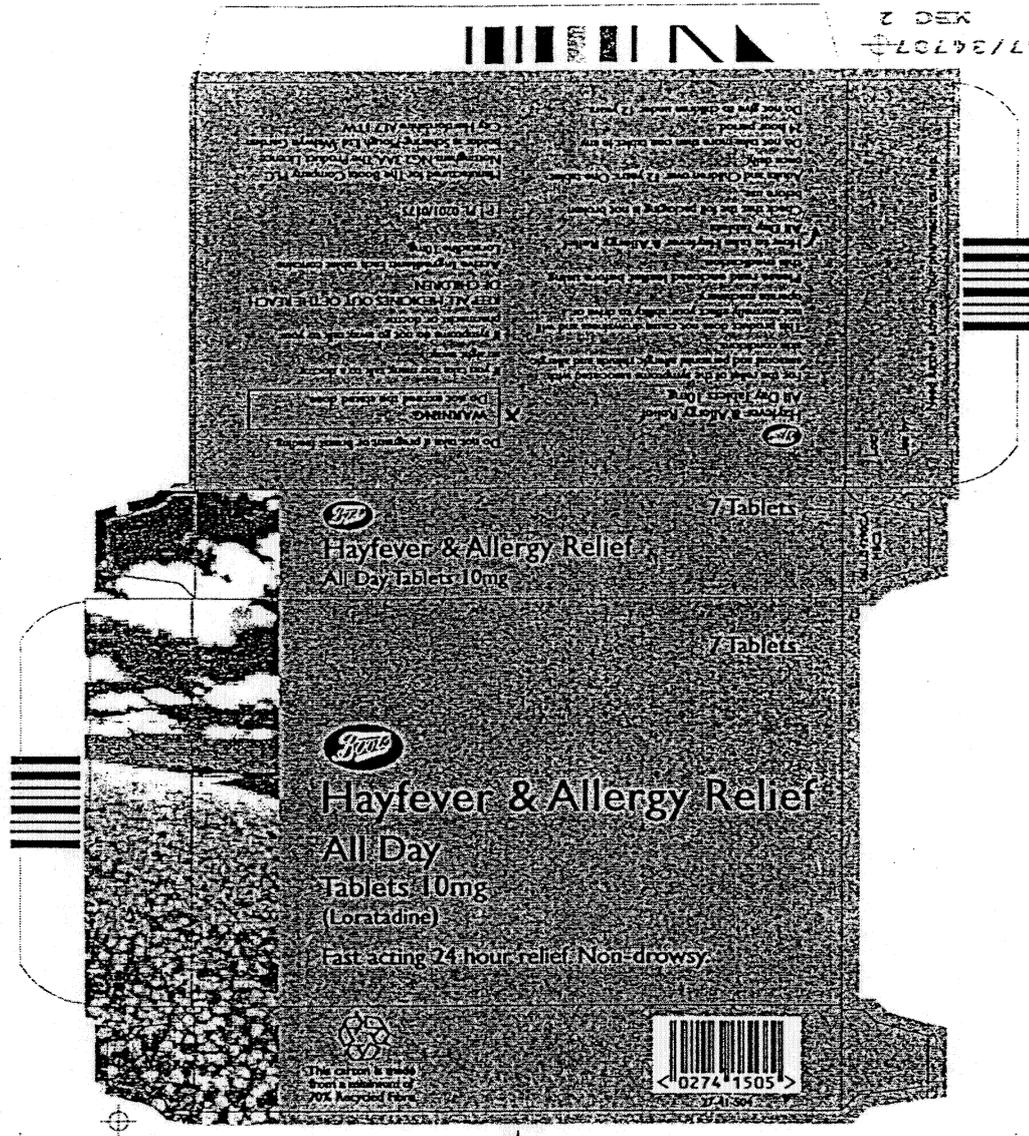
If there is anything about *Claritin Allergy* syrup you do not understand or are unsure about, your doctor or pharmacist will be able to help or advise you.

Date of revision of this leaflet: October 2000



United Kingdom

2 DEX
S/5667/34707



Hayfever & Allergy Relief
All Day Tablets 10mg

7 Tablets



Hayfever & Allergy Relief
All Day
Tablets 10mg
(Loratadine)

7 Tablets

Fast acting 24 hour relief Non-drowsy



This carton is made
from a minimum of
70% Recycled fibre



0274 1505

United Kingdom



Hayfever & Allergy Relief All Day Tablets

00U56G6SINR

The name of your medicine is Hayfever & Allergy Relief All Day Tablets.

Each tablet contains Loratadine 10mg as the active ingredient.

Also contains: Lactose, Maize Starch, Magnesium Stearate.

Each pack contains 7 tablets.

Hayfever & Allergy Relief All Day Tablets belong to a group of medicines called antihistamines which help relieve symptoms associated with seasonal and perennial allergic rhinitis.

Manufactured for The Boots Company PLC Nottingham NG2 3AA by Schering-Plough Labo N.V. Heist-op-den-Berg Belgium The Product Licence holder is Schering-Plough Ltd Shire Park Welwyn Garden City Hertfordshire AL7 1TV.

What is your medicine for?

Hayfever & Allergy Relief All Day Tablets are for the relief of symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching and burning and itching of the eyes. They are also indicated for the relief of symptoms associated with chronic urticaria of unknown origin.

Before taking your medicine

Do not take Hayfever & Allergy Relief All Day Tablets if you are pregnant, planning to become pregnant or are breast feeding.

You must tell your pharmacist or doctor if the answer to the following question is YES.

Are you allergic to any of the ingredients shown above?

There have been no reports of undesirable effects occurring when Loratadine has been taken at the same time as some other medicines.

However, before you start taking these tablets, you should tell your doctor or pharmacist if you are taking medicines for any other illness or condition.

If in doubt, talk to your pharmacist or doctor.

How to take your medicine

Check that the foil packaging is not broken before use.

Adults and Children over 12 years:
One tablet once daily.

Do not take more than one tablet in any 24 hour period.

Do not give to children under 12 years.

DO NOT EXCEED THE STATED DOSE

What if you take too many?

If you take too many tablets, talk to a doctor or a hospital casualty department straight away. Take your tablets with you.

After taking your medicine

As with most medicines Hayfever & Allergy Relief All Day Tablets can sometimes cause side effects.

Tests have shown that these tablets do not cause drowsiness, however, there may be rare exceptions. Make sure that you are not affected in this way before driving or carrying out tasks requiring concentration. Rare effects reported include fatigue, nausea, headache, loss of hair, allergic reaction, abnormal heart rate, fainting and liver changes.

If concerned or anything else unusual happens, talk to your pharmacist or doctor.

If symptoms do not go away, talk to your pharmacist or doctor.

Storing your medicine

Do not take your tablets after the "Use by" date. Keep them in their original pack.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN, PREFERABLY IN A LOCKED CUPBOARD

If you have any questions or are not sure about anything, ask your pharmacist or doctor. They can obtain additional information about this medicine if necessary.

Leaflet revised June 1999.

GLUE STRIP

ID BAR CODE

Once Daily / Non-Drowsy
Claritin
24 Hour Tablets

Once Daily / Non-Drowsy Claritin 24 Hour Tablets

Warnings (continued)
Do not use for allergic skin reaction or hives unless you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria). Do not use to treat food or drug allergies or insect bites or stings.

Drug Facts
Active ingredient (in each tablet) Antihistamine Loratadine 10 mg.

Uses
temporarily relieves the following symptoms due to hay fever or other upper respiratory allergies without causing drowsiness:
sneezing
runny nose
itchy, watery eyes
itchy throat or nose
relieves and reduces itching and rash due to recurring or chronic hives of an unknown source; however, only use this product for itching and rash after being told by a doctor that you have recurring or chronic hives (chronic idiopathic urticaria).

Warnings
Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:
trouble swallowing
trouble breathing
trouble speaking
joint pain
hives or swelling in or around mouth

Allergy Alert: Do not use if you are allergic to Claritin (loratadine) or other antihistamines.

Other information
store between 7° and 30° C (35° and 85° F)
protect from excessive moisture
do not use if the individual blister unit is open or torn

Inactive ingredients
corn starch, lactose, magnesium stearate

Once Daily / Non-Drowsy
Claritin
24 Hour Tablets

Once Daily / Non-Drowsy
Claritin[®]
Antihistamine/Loratadine 10mg
24 Hour Tablets

Allergy

Non-Sedating Relief of

- Sneezing • Itchy, Watery Eyes
- Runny Nose • Itchy Throat or Nose
- Itching and Rash Due to Recurring or Chronic Hives

Full Prescription Strength 10 Tablets

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recyclable carton

0 0000-0000-00 0

ID BAR CODE

Once Daily / Non-Drowsy
Claritin
24 Hour Tablets

GLUE STRIP

ID BAR CODE

Once Daily / Non-Drowsy
Claritin[®]
24 Hour Tablets



U.S. 273

Once Daily / Non-Drowsy
Claritin[®]
24 Hour Tablets

Drug Facts
Loratadine 10 mg, Antihistamine
Active ingredient (in each tablet) Purpose

Uses
relieves and reduces itching and rash due to recurring or chronic hives of an unknown source.
use only after being told by a doctor that you have recurring or chronic hives of an unknown source.
(chronic idiopathic urticaria).

Warnings
Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:
trouble swallowing
trouble speaking
fever above 100°F
wheezing or problems breathing
hives or swelling in or around mouth
Allergy Alert: Do not use if you are allergic to Claritin (loratadine) or other antihistamines.

Do not use unless you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria).

Drug Facts (continued)

Warnings (continued)

Do not use to treat food or drug allergies or insect bites or stings.

Ask a doctor before use if you have liver disease, are pregnant or breast-feeding, have kidney disease, or are taking other medicines.

Do not give to children under 6 years of age unless directed by a doctor.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
adults and children 6 years and over: 1 tablet every 24 hours. Do not exceed 1 tablet in 24 hours.
children under 6 years of age: ask a doctor.

Other information
store between 2° and 30° C (36° and 86° F)
protect from excessive moisture
do not use if the individual blister unit is open or torn

Inactive ingredients
corn starch, lactose, magnesium stearate

Once Daily / Non-Drowsy
Claritin[®]
24 Hour Tablets

Once Daily / Non-Drowsy
Claritin[®]
Antihistamine/Loratadine 10mg
24 Hour Tablets

Recurring Hives
Relieves and Reduces ITCHING & RASH
Due to Recurring or CHRONIC HIVES

Full Prescription Strength

10 Tablets

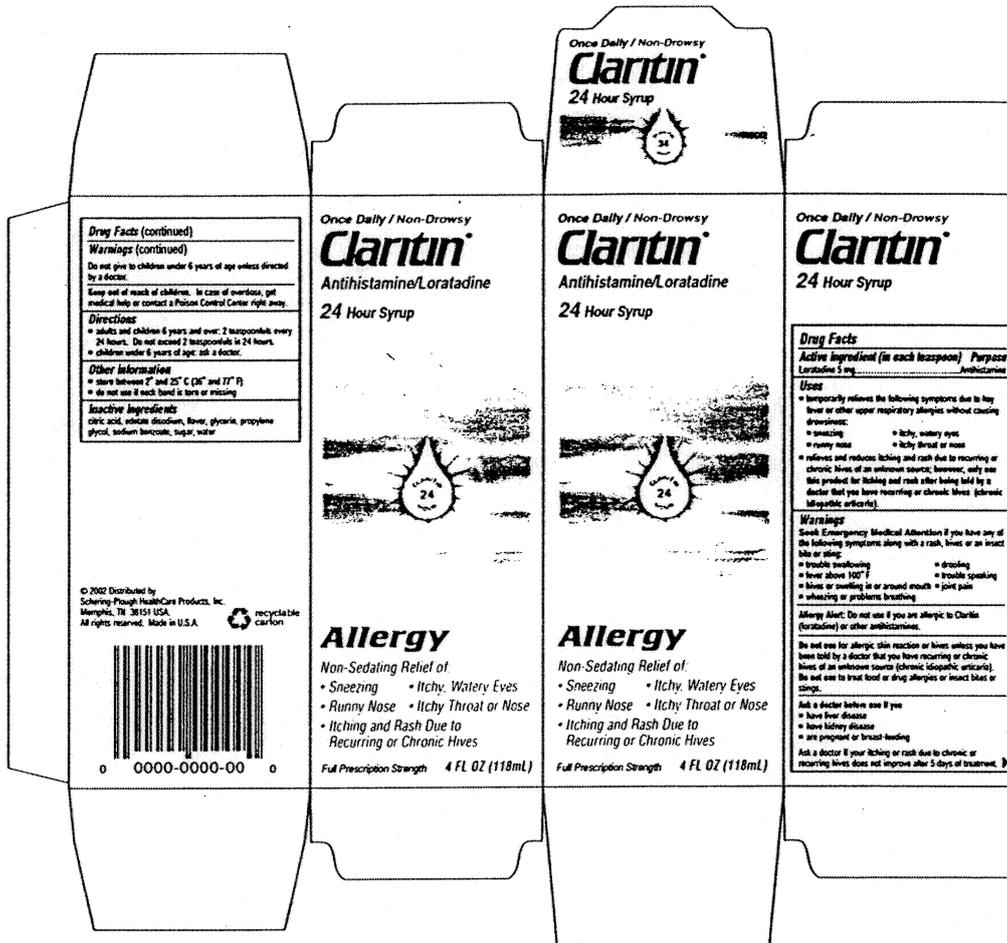
ID BAR CODE

Once Daily / Non-Drowsy
Claritin[®]
24 Hour Tablets



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Drug Facts (continued)

Warnings (continued)

Do not give to children under 6 years of age unless directed by a doctor.
 Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

• adults and children 6 years and over: 2 teaspoonsful every 24 hours. Do not exceed 2 teaspoonsful in 24 hours.
 • children under 6 years of age: ask a doctor.

Other information

• store between 2° and 25° C (32° and 77° F)
 • do not use if each band is torn or missing

Inactive ingredients

citric acid, sodium disodium, flavor, glycerin, propylene glycol, sodium benzoate, sugar, water

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Once Daily / Non-Drowsy
Clartin
 Antihistamine/Loratadine
 24 Hour Syrup



Allergy

Non-Sedating Relief of

- Sneezing • Itchy, Watery Eyes
- Runny Nose • Itchy Throat or Nose
- Itching and Rash Due to Recurring or Chronic Hives

Full Prescription Strength 4 FL OZ (118mL)

Once Daily / Non-Drowsy
Clartin
 24 Hour Syrup



Once Daily / Non-Drowsy
Clartin
 Antihistamine/Loratadine
 24 Hour Syrup



Allergy

Non-Sedating Relief of

- Sneezing • Itchy, Watery Eyes
- Runny Nose • Itchy Throat or Nose
- Itching and Rash Due to Recurring or Chronic Hives

Full Prescription Strength 4 FL OZ (118mL)

Once Daily / Non-Drowsy
Clartin
 24 Hour Syrup

Drug Facts

Active ingredient (in each teaspoon) Purpose
 Loratadine 5 mg Antihistamine

Uses

- temporarily relieves the following symptoms due to hay fever or other upper respiratory allergies without causing drowsiness:
 - sneezing
 - itchy, watery eyes
 - runny nose
 - itchy throat or nose
- relieves and reduces itching and rash due to recurring or chronic hives of an unknown source; however, only use this product for itching and rash after being told by a doctor that you have recurring or chronic hives (chronic idiopathic urticaria).

Warnings

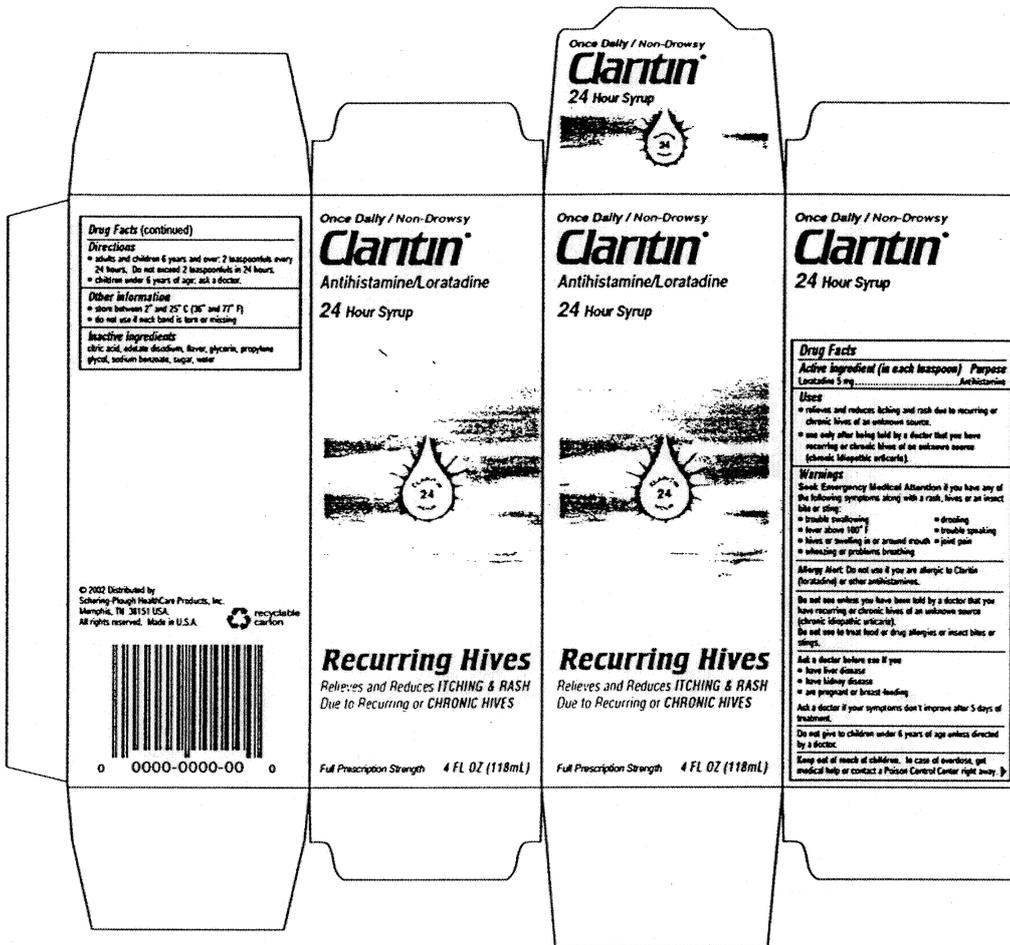
Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:
 • trouble swallowing • drooping
 • fever above 102° F • trouble speaking
 • hives or swelling in or around mouth • joint pain
 • wheezing or problems breathing

Allergy Alert: Do not use if you are allergic to Clartin (loratadine) or other antihistamines.

Do not use for allergic skin reaction or hives unless you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria). Do not use to treat food or drug allergies or insect bites or stings.

Ask a doctor before use if you
 • have liver disease
 • have kidney disease
 • are pregnant or breast-feeding

Ask a doctor if your itching or rash due to chronic or recurring hives does not improve after 3 days of treatment. 



Drug Facts (continued)

Directions

- adults and children 6 years and over: 2 teaspoons every 24 hours. Do not exceed 2 teaspoons in 24 hours.
- children under 6 years of age: ask a doctor.

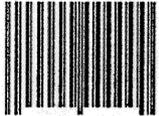
Other information

- store between 2° and 22° C (36° and 72° F)
- do not use if neck band is torn or missing

Inactive ingredients

citric acid, edetate disodium, flavor, glycerin, propylene glycol, sodium benzoate, sugar, water

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Once Daily / Non-Drowsy
Clartini
Antihistamine/Loratadine
24 Hour Syrup



Recurring Hives
Relieves and Reduces **ITCHING & RASH**
Due to Recurring or **CHRONIC HIVES**

Full Prescription Strength 4 FL OZ (118mL)

Once Daily / Non-Drowsy
Clartini
24 Hour Syrup



Once Daily / Non-Drowsy
Clartini
Antihistamine/Loratadine
24 Hour Syrup



Recurring Hives
Relieves and Reduces **ITCHING & RASH**
Due to Recurring or **CHRONIC HIVES**

Full Prescription Strength 4 FL OZ (118mL)

Once Daily / Non-Drowsy
Clartini
24 Hour Syrup

Drug Facts

Active ingredient (in each teaspoon)	Purpose
Loratadine 5 mg	Antihistamine

Uses

- relieves and reduces itching and rash due to recurring or chronic hives of an unknown source.
- use only after being told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria).

Warnings

Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:

- trouble breathing
- dizziness
- fever above 100°
- trouble speaking
- hives or swelling in or around mouth
- joint pain
- wheezing or problems breathing

Allergy Alert: Do not use if you are allergic to Clartini (Loratadine) or other antihistamines.

Do not use unless you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria). Do not use to treat food or drug allergies or insect bites or stings.

Ask a doctor before use if you:

- have liver disease
- have kidney disease
- are pregnant or breast feeding

Ask a doctor if your symptoms don't improve after 5 days of treatment.

Do not give to children under 6 years of age unless directed by a doctor.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

<p>Warnings (continued)</p> <p>Do not use to treat food or drug allergies or insect bites or stings.</p> <p>Ask a doctor before use if you:</p> <ul style="list-style-type: none"> • have any disease • are pregnant or breast-feeding • take a doctor before use if you: 	
<p>Drug Facts</p> <p>24 Hour RediTab[®] Rapidly-dissintegrating Tablets</p> <p>Active Ingredient (in each tablet)</p> <p>Loratadine 10 mg Antihistamine</p>	
<p>Uses</p> <p>temporarily relieves the following symptoms due to hay fever or other upper respiratory allergies without causing drowsiness:</p> <ul style="list-style-type: none"> • sneezing • itchy, watery eyes • itchy throat or nose <p>relieves and reduces itching and rash due to recurring or chronic hives or an itchy skin that you have itching or chronic hives (hives) (swallowable tablets)</p>	
<p>Warnings</p> <p>Make Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:</p> <ul style="list-style-type: none"> • trouble swallowing • trouble speaking • trouble breathing • fever above 100° F • hives or swelling in or around mouth • joint pain <p>Allergy Alert: Do not use if you are allergic to Claritin (loratadine) or other antihistamines.</p> <p>Do not use for allergic skin reactions or chronic hives of an unknown source (chronic idiopathic urticaria).</p>	
<p>Other Information</p> <ul style="list-style-type: none"> • store between 7° and 25° C (41° and 77° F) • keep in a dry place • do not use if blister foil envelope or individual blister unit inside the envelope is open or torn • use within 6 months of opening foil envelope <p>Inactive Ingredients</p> <p>citric acid, gelatin, mannitol, methyl paraben</p>	

Once Daily / Non-Drowsy
Claritin
 24 Hour RediTab[®]
 Rapidly-dissintegrating Tablets

Once Daily / Non-Drowsy

Claritin

24 Hour RediTab[®]
Rapidly-dissintegrating Tablets

Once Daily / Non-Drowsy

Claritin

Antihistamine/Loratadine 10mg

24 Hour RediTab[®]
Rapidly-dissintegrating Tablets

Allergy

Non-Sedating Relief of:

- Sneezing
- Itchy, Watery Eyes
- Runny Nose
- Itchy Throat or Nose
- Itching and Rash Due to Recurring or Chronic Hives

Full Prescription Strength

10 RediTab[®] Tablets

Once Daily / Non-Drowsy

Claritin

24 Hour RediTab[®]
Rapidly-dissintegrating Tablets

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recyclable carbon



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Once Daily / Non-Drowsy
Claritin
 24 Hour RediTab[®]
 Rapidly-dissintegrating Tablets



Once Daily / Non-Drowsy

Claritin

24 Hour RediTabs[®]
Rapidly-disintegrating Tablets

<p>Drug Facts (continued)</p> <p>Warnings (continued)</p> <p>Ask a doctor before use if you</p> <ul style="list-style-type: none"> have ever had any other allergic reaction to any medication or food, drink, or product <p>Do not give to children under 6 years of age unless directed by a doctor.</p> <p>Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p> <p>Directions</p> <ul style="list-style-type: none"> Adults and children 6 years and over: 1 RediTab[®] tablet every 24 hours. Do not exceed 1 RediTab[®] tablet in 24 hours. Place 1 RediTab[®] tablet on tongue. Tablet disintegrates rapidly, with or without water. Children under 6 years of age: ask a doctor. <p>Other Information</p> <ul style="list-style-type: none"> Keep in a dry place. Do not use if metered dose container or individual blister unit inside the envelope is open or torn. Do not use if metered dose container or individual blister unit inside the envelope is open or torn. Use RediTab[®] tablet immediately after opening individual blister unit. <p>Inactive Ingredients</p> <p>One acid, gelatin, mannitol, malt flavor</p>	<p>24 Hour RediTab[®] Rapidly-disintegrating Tablets</p> <p>Claritin Once Daily / Non-Drowsy</p> <p>Drug Facts</p> <p>Active Ingredient (in each tablet)</p> <p>Loratadine 10 mg</p> <p>Purpose</p> <p>Antihistamine</p> <p>Uses</p> <p>Relieves and reduces itching and rash due to recurring or chronic hives of an unknown source.</p> <p>Use only after being told by a doctor that you have recurring or chronic hives of an unknown source.</p> <p>Warnings</p> <p>Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:</p> <ul style="list-style-type: none"> trouble swallowing trouble speaking trouble breathing trouble breathing in or around mouth feeling faint <p>Warnings</p> <p>Do not use if you are allergic to Claritin (loratadine) or other antihistamines.</p> <p>Do not use if you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria).</p> <p>Do not use to treat food or drug allergies or insect bites or stings.</p>
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Once Daily / Non-Drowsy

Claritin[®]

24 Hour RediTabs[®]
Rapidly-disintegrating Tablets



Once Daily / Non-Drowsy
Claritin[®]
24 Hour RediTabs[®]
Rapidly-disintegrating Tablets

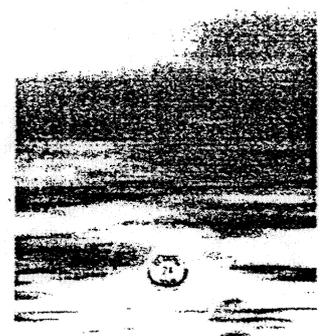


Once Daily / Non-Drowsy

Claritin[®]

Antihistamine/Loratadine 10mg

24 Hour RediTabs[®]
Rapidly-disintegrating Tablets



Recurring Hives

Relieves and Reduces **ITCHING & RASH**
Due to Recurring or **CHRONIC HIVES**

Full Prescription Strength

10 RediTabs[®] Tablets

Once Daily / Non-Drowsy

Claritin[®]

24 Hour RediTabs[®]
Rapidly-disintegrating Tablets

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4 3/8w X 1 3/16h X 3 1/8d

<p>Drug Facts</p> <p>Active ingredients (in each tablet)</p> <p>Loratadine 10 mg: Antihistamine Pseudoephedrine sulfate 240 mg: Nasal decongestant</p>	
<p>Uses</p> <p>temporarily relieves the following symptoms due to hay fever or other upper respiratory allergies without causing drowsiness:</p> <ul style="list-style-type: none"> nasal congestion runny nose itchy throat or nose itchy, watery eyes <p>temporarily restores free breathing through the nose</p> <ul style="list-style-type: none"> relieves sinus pressure reduces swelling of nasal passages 	
<p>Warnings</p> <p>Do not use 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 do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.</p> <p>Allergy Alert: Do not use if you are allergic to Claritin (loratadine) or other antihistamines.</p>	
<p>Other information</p> <ul style="list-style-type: none"> do not use if the individual blister unit is open or torn protect from excessive moisture store between 15° and 25° C (59° and 77° F) 	
<p>Inactive ingredients</p> <p>silicon dioxide, sugar, titanium dioxide, polyethylene glycol, povidone, calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone.</p>	

Once Daily / Non-Drowsy
Claritin-D
 24 Hour Extended Release Tablets

Once Daily / Non-Drowsy

Claritin-D

24 Hour Extended Release Tablets

Once Daily / Non-Drowsy

Claritin-D[®]

Antihistamine/Loratadine 10mg
Decongestant/Pseudoephedrine Sulfate 240mg

24 HOUR
Extended Release Tablets

Allergy & Congestion

Non-Sedating Relief Of:

- Nasal & Sinus Congestion
- Itchy, Watery Eyes
- Sneezing
- Itchy Throat or Nose
- Runny Nose

Full Prescription Strength 10 Extended Release Tablets

Once Daily / Non-Drowsy

Claritin-D[®]

24 Hour Extended Release Tablets

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Once Daily / Non-Drowsy
Claritin-D
 24 Hour Extended Release Tablets