

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 341]

[Docket No. 76N-0052]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC
Cold, Cough, Allergy, Bronchodilator and
Antiasthmatic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products; comments by December 8, 1976.

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on March 3, 1976, the report of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein. After a careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 12, 1976, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document and will probably be revised downward.

This proposal sets forth the conclusion of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products that several ingredients are safe and effective for OTC use which heretofore have been limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. The Commissioner is aware that

a number of questions have been presented to the agency regarding the OTC marketing status of ingredients in amounts of ingredients previously limited to prescription use prior to finalization of an applicable monograph for the ingredients. The reclassification of ingredients from prescription to OTC status presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug) and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 FEDERAL REGISTER that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients proposed for Category I, e.g., ingredients having manufacturing or formulation problems or unresolved questions concerning a potential for abuse or misuse; and he may make a tentative determination that an approved new drug application (NDA) is required for marketing an OTC product containing such ingredients. The Commissioner acted on this proposal by final regulation published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580).

The Commissioner has reviewed those ingredients included in the 1975 recommendations that are currently in prescription use or classified for use at a dosage level lower than recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.5 milligrams (mg), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be considered generally recognized as safe and effective for OTC use as an antitussive until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antitussive product containing diphenhydramine. The Commissioner has made an initial determination to accept the Panel's recommendations on OTC use of a number of ingredients among which are chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. However, the Commissioner wishes to raise several pertinent points regarding these drugs, and they are fully explained below.

Promethazine. The Panel recommended classification of the ingredient promethazine as a Category I OTC antihistaminic drug. This ingredient is presently a component of drug products that are the subject of approved NDA's for prescription use as antihistamines, as

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for anticholinergic drugs. (See part VI, paragraph C. below—Data Required for Evaluation.)

REFERENCE

Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 542, 1970.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for anticholinergics. Additional data are required to support the following anticholinergic claim: a. "Prolongs relief by helping to prevent further swelling and irritation."

b. The Panel concludes that claims relating to duration of action, e.g. "all day", "all night", "for hours", will require documentation.

c. *Claims that sleep will be facilitated.* These include claims such as "helps you fall asleep" and "for restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing anticholinergic drugs.* a. *General principles.* Effectiveness of an anticholinergic drug should be determined by the ability to reduce rhinorrhea (excessive watery nasal secretions) in patients with acute or chronic rhinitis. Tests should involve double-blind placebo controlled assessment of the ability of the drug to decrease watery nasal secretions and/or tearing when administered orally and increase the comfort of the patient. This evaluation must be a subjective one since there is no technique for objective measurements. The dosage, intervals of administration and conditions for the trials should be identical to the labeled recommendations.

b. *Selection of patients.* Selection of patients for treatment should be based on the diagnosis of rhinitis with rhinorrhea. Patients with chronic allergic or vasomotor rhinitis may present more stable symptoms but in most patients rhinorrhea is a variable and inconstant symptom. Because of this, a large number of suitable patients, e.g., approximately 50 subjects depending upon the protocol, must be used and assigned in a random fashion to placebo or drug groups. Further, these groups should be matched by age and sex, and if possible, by severity of symptom. It is also highly desirable to control conditions of temperature and humidity.

c. *Methods of study.* There is nothing in the literature concerning techniques testing rhinorrhea and it is possible

that a subjective method could be developed. It might be possible to semi-quantitate the degree of rhinorrhea by weighing tissues or handkerchiefs; the wet weight minus the dry weight would be a rough index of the amount of secretions per unit of time. The subjects should be evaluated on the basis of the severity of the rhinorrhea and the subject's appraisal of his discomfort. Numerical values should be assigned indicating increasing severity. A double-blind technique is used for patients with acute rhinitis and in chronic rhinitis with rhinorrhea a double-blind crossover design. Observation should be carried out for 3 to 5 days to determine the extent of possible side effects.

d. *Interpretation of data.* The data should be subjected to statistical analysis and a p value of 0.05 or less would be acceptable as evidence of drug action.

Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

VII. ANTIHISTAMINES

A. GENERAL DISCUSSION

1. *Development.* The antihistamines were developed in France from a series of compounds with pronounced antihistaminic activity in the laboratory but which were too toxic for clinical use. One of these antihistaminic drugs, Antergan, was used for the first time clinically in 1942 in France. This was promptly followed by pyrilamine maleate. There then followed in 1946 the appearance in the United States of diphenhydramine and tripeleminamine (Ref. 1). Many active antihistamine drugs appeared soon thereafter and the total number currently marketed is probably now close to fifty.

REFERENCE

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542-573, 1947.

2. *Mechanism of action.* The antihistamines are useful primarily for the symptomatic relief of certain allergic disorders (Refs. 2 through 5). They suppress symptoms presumably caused by the release of histamine and possibly other chemical mediators from mast cells in mucous membranes (Refs. 1, 2, 5, and 6). Histamine attaches to specific receptor sites at the surface of cells in the nose, eyes, lungs, and skin and causes characteristic "allergic" symptoms. The antihistamines appear to act by competing with histamine for the receptor sites. If the antihistamine reaches the receptor site first, histamine is blocked from initiating a response. In this manner, antihistamines effectively block most smooth muscle responses to histamine.

The antihistaminic drugs are well tolerated by laboratory animals and produce recognizable effects on blood pressure, heart rate or respiration when given in large oral doses. These effects are more pronounced if the drugs are given intravenously (Refs. 2 and 5).

In man, the involvement of renal (kidney), hepatic (liver), hematologic (blood) or other major body systems in adverse reactions appears to be remarkably uncommon (Refs. 5 and 7).

In the skin of man, antihistamines inhibit the wheal, flare and itch reaction that occurs within a few minutes after the injection of histamine intracutaneously (into the skin). The antihistaminic drugs also inhibit similar reactions mediated by antibodies belonging to the IgE class of immunoglobulins (antibodies), but to a somewhat lesser degree. The Panel has previously discussed the role of antibodies in allergy earlier in this document. (See part II, paragraph B.1. above—Allergy.) Examples of reactions mediated by antibodies of the IgE class are those produced by skin testing with pollen extracts in which histamine release is involved. In addition to histamine, there are other chemical mediators released in IgE mediated reactions, and the antihistaminic drugs antagonize these much less effectively if at all. It is probably for this reason that these drugs are more active in protecting against the effects of injected histamine than in protecting against anaphylaxis in animals or allergic symptoms in man.

REFERENCES

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542-573, 1947.

(2) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635-642, 1970.

(3) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491-492, 1973.

(4) "Antihistamine Drugs," in "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

(5) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(6) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," in "Drill's Pharmacology in Medicine," 4th Ed., Edited by Djalma, McGraw Hill Co., New York, pp. 995-1020, 1971.

(7) Wyngaarden, J. B. and M. H. SeEVERS, "The Toxic Effects of Antihistamine Drugs," *Journal of the American Medical Association*, 145:277-282, 1951.

3. *Preclinical studies.* As a group the antihistamines have the capacity to decrease or suppress effects produced by histamine in animals (Refs. 1 through 4). Animal "models" are therefore useful in determining drugs which will have antihistamine activity. An animal commonly used is the guinea pig. Guinea pigs can be protected by an antihistaminic drug from the often fatal narrowing of the air passages in the lung (bronchoconstriction) produced by histamine which causes death by asphyxia. Likewise, contraction of isolated tissues

of the guinea pig intestine (ileum) and of the airways of the trachea and bronchus produced by histamine is prevented by antihistamines in *in vitro* studies. These effects are most easily demonstrated in the guinea pig because of the animal's intense sensitivity to histamine but the antihistaminic drugs also act in a similar manner in some other laboratory animals and in man (Refs. 1 through 3).

The antihistaminic drugs are somewhat protective in experimental allergic reactions (anaphylaxis) but their action here is not so intense as their action against histamine. Apparently in man, some allergic reactions (hay fever and hives) are caused entirely or in large part by histamine release whereas other reactions, for example asthma, are not. The capacity to block the symptom-producing effects of histamine presumably explains why antihistamines are effective in relieving the symptoms of hay fever and hives (consisting of rashes associated with itching wheals) in which release of histamine appears to be the main cause of the symptoms (Refs. 2 and 3).

In concentrations that are effective against the spasmogenic activity of histamine, antihistamines have little or no capacity to counter the spasmogenic activity of other drugs such as acetylcholine, nicotine or barium.

Gastric ulcers with perforation have occurred in guinea pigs receiving both histamine and antihistamine under highly artificial conditions (Ref. 3). The experiment depends on the fact that antihistamine drugs can protect against histamine-induced bronchospasm and asphyxia although the antihistaminic drugs do not prevent another action of histamine which is to stimulate the production of acid within the stomach. Under the conditions of the experiment, increased acid production is induced in the guinea pig by giving large doses of histamine. The antihistamine protects the guinea pig from bronchospasm and fatal asphyxia which the histamine would otherwise cause. The Panel finds, therefore, that the antihistaminic drugs play no ulcer-producing role in this type of experiment and there are no other data which would implicate the antihistaminic drugs in promoting acid production in the stomach or ulcer.

In view of the chemical heterogeneity of the antihistamines, there is a surprising unanimity among the statements of critical investigators and authorities in describing their antihistaminic actions. The antihistamines under consideration are described as being intense antagonists of histamine, are of low acute (Ref. 1) and chronic (Ref. 2) toxicity and most are effective in suppressing the symptoms of allergic rhinitis (Refs. 1, 2, 3, 5, and 6). It is because these attributes are shared by most or all of the antihistamine drugs that individual drugs are not often singled out for special attention in the texts reviewed.

REFERENCES

- (1) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," in "Drill's

Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995-1020, 1971.

(2) Beckman, H., "Pharmacology: The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635-642, 1970.

(4) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542-573, 1947.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491-492, 1973.

(6) "Antihistamine Drugs," in "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

4. *Common side effects.* Among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to chemical class (Refs. 1 through 3). With the exception of phenindamine, all the antihistamines considered by the Panel cause central nervous system depression, often recognized as drowsiness (sedation). Drowsiness is most marked among the antihistamines from the chemical class known as the ethanolamines, e.g., diphenhydramine, doxylamine and phenyltoloxamine, and least marked among the alkylamines, e.g., chlorpheniramine, brompheniramine, and pheniramine. The ethylenediamines, e.g., methapyrilene, pyrilamine maleate, thenyldiamine and thonzylamine, are intermediate in this respect.

There is a wide range of susceptibility to actions of the antihistaminic drugs especially as regards the central nervous system. The chief danger from overdosage of antihistamines is central nervous system depression. The ethanolamines, (e.g., diphenhydramine and doxylamine) and the ethylenediamines, (e.g., methapyrilene) are also used as mild sleep inducers, and the ethanolamines, (e.g., diphenhydramine and dimenhydrinate) and the ethylenediamines, (e.g., methazine) as antiemetics for the treatment of the symptoms of motion sickness. Some are useful in treating paralysis agitans and petit mal seizures. No exact explanation for these actions is available.

Stimulation of the central nervous system has been observed in patients with focal cortical lesions in whom small doses of antihistamines may cause electroencephalographic activity and even frank seizures (Ref. 4). However, the precise basis for this stimulation is not fully understood. Excessive doses in any patient may cause restlessness, excitation, delirium, tremors, and even convulsions (Refs. 1 through 3). Phenindamine causes stimulation rather than depression as a common side effect and is unique in this respect among the antihistamines under consideration. The Panel has discussed this side effect observed with phenindamine later in this document. (See part VII. paragraph B.1.f. below—Phenindamine tartrate.)

Dryness of the mouth is also a common side effect of the antihistaminic drugs.

Other side effects which are not as common as drowsiness have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects such as anorexia (appetite loss), nausea, vomiting, epigastric distress, constipation or diarrhea (Ref. 1).

Also reported are cardiovascular symptoms which may include palpitations, hypotension, headache or tightness of the chest (Ref. 1). In the genitourinary system, an effect on the frequency of urination and/or dysuria may be encountered (Ref. 1). Cutaneous side effects such as urticarial, eczematous, bullous, or petechial rashes and photosensitivity may occur (Ref. 5). Hematologic complications that have been reported have included rare occurrences of pancytopenia, thrombocytopenia, hemolytic anemia and agranulocytosis (Ref. 5).

The Panel concludes 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.

REFERENCES

(1) Douglas, W. W., "Histamine and Antihistamine; 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635-642, 1970.

(2) Beckman, H., "Pharmacology: The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," in "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995-1020, 1971.

(4) King, G. and S. D. Weeks, "Pyrilamine Activation of the Encephalogram, EEG," *Clinical Neurophysiology*, 18:503, 1965.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491-492, 1973.

5. *Reduction of nasal secretions.* A common but variable action of the antihistaminic drugs is their anticholinergic effect of reducing nasal secretions. Some patients describe this as a disagreeable drying effect. In the recommended dosage, the drying effect of most antihistamines is less intense than that of atropine. This action appears to be entirely palliative and does not alter or shorten the course of the illness. The Panel is aware that a controversy exists concerning the use of antihistamines in patients with bronchial asthma where a "drying action" is undesirable. Many physicians consider this effect to be disadvantageous in patients with bronchial asthma and some maintain that the antihistaminic drugs are contraindicated in patients with this disease.

It is the view of the Panel that in the presence of allergic rhinitis and in the "common cold," secretions are often excessive and a "drying" agent may then be appropriate. However, the Panel finds, as do other investigators, that effectiveness of antihistamines widely used in the "common cold" has not been demonstrated in controlled studies (Ref. 1). In

addition, the Panel concludes that there is no evidence that release of histamine is either the cause of symptoms in the "common cold" nor is histamine release a significant factor in the "common cold." This will be discussed more fully below. (See part VII. paragraph C.2. below—Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold.")

REFERENCE

(1) West, S., B. Brandon, P. Stolley and R. Rumrill, "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100-107, 1975.

6. *Human toxicity.* Unlike other classes of drugs, the extensive clinical experience with antihistamines has fairly well identified virtually all of the central nervous system manifestations of toxicity. The Panel has extensively reviewed these known toxic symptoms. While many of the more severe symptoms of antihistamines are relatively rare or are due to large doses or accidental overdose, the Panel has included them in the interest of completeness of this review.

Although rare, fatal or near fatal doses cause fixed, dilated pupils; muscular twitching followed by convulsions, sometimes with opisthotonos; coma; circulatory collapse; and respiratory failure. Convulsions may persist for 24 hours, coma for several days. Death rarely occurs later than 24 hours after ingestion unless due to infection associated with agranulocytosis (Ref. 1).

Because of the unique nature and wide use of antihistaminic drugs and because of the lack of extensive well-controlled clinical studies, the Panel has reviewed adverse reaction reporting systems to obtain a better understanding of the safety of antihistamines. Two major sources of data are the adverse reaction files of the Food and Drug Administration and the latest Poison Control Studies of the National Clearinghouse for Poison Control Centers. Since antihistamines have been extensively marketed for nearly 30 years, the Panel believes that a review of adverse reactions reports will serve as an indication of their safety.

It should be emphasized that these information sources are not entirely accurate nor do they necessarily give a valid picture of the incidence or prevalence of particular side effects. However, these reporting mechanisms do highlight the types of adverse reactions that can be expected. Where massive overdoses are ingested, such as in suicide attempts, these reports give a clearer picture of an ingredient's toxicological profile, significant elements of which include morbidity levels, toxic reactions which occur at varying dosage levels as well as dosage levels at which reversibility of an ingredient's toxic effects may occur.

The latest "Poison Control Statistics," published by the National Clearinghouse for Poison Control Centers provides the latest published data now available and covers the period from January to December, 1973 (Ref. 2). This publication presents collective toxicity data on household products and medicines from

the Nation's 580 Poison Control Centers. This information reflects the treatment or response to each telephone inquiry to the Poison Control Centers concerning a poisoning or accidental ingestion and usually is not verified for accuracy except for the more obvious incongruities. Although only 1973 statistics were reviewed in detail by the Panel, that particular year is considered representative of all the years for which this type data was compiled.

Unlike the Poison Control Center data the adverse reaction data compiled by the Food and Drug Administration are cumulative and represent the total number of reported cases since the reporting system was implemented in 1968. Adverse reactions are reported to the agency in a variety of ways and at various levels of sophistication. These sources include hospitals, physicians, pharmaceutical manufacturers, consumers, or Food and Drug Administration personnel who often obtained these reports from consumers and physicians. While some of the data are verified for accuracy, they are often incomplete. Data are reported as having one of four causal relationships: directly related, probably related, possibly related and remotely related. For the Panel's purposes, only the adverse reactions which are directly or probably related to drug ingestion are discussed. The Panel recognizes that the statistics generated by the Poison Control Center and the Food and Drug Administration can be misleading and must be carefully used in determining the potential health threat of ingredients to consumers because the extenuating circumstances of each individual case are not represented.

A review of these two sources reveals several variables in the collection and comprehensiveness of the data which must be taken into consideration for a realistic view of the statistics compiled. For example, in the Poison Control Center data, few of the ingestions were of a single chemical entity. Most ingestions were of multi-ingredient products identified by brand name or conversely were ingestion of multiple products. Thus, it is improper to clearly attribute the symptom(s) reported to any one ingredient contained in a product. Further, in some cases no clear delineation of the quantity or number of units of an agent ingested is given. These data were often incomplete and left blank or "unknown" on the document. Of those listing a quantity, several were found to be at normal or subnormal dosage levels with no symptoms exhibited. These cases are included in the Poison Control Statistics as a reported "poisoning" when in fact no "poisoning" occurred. In addition, reported cases of hospitalization allude to symptoms serious enough to require treatment in a hospital, but give no indication whether the patient was seen only at the emergency room or actually admitted for treatment. Many of these same weaknesses and inconsistencies in data collection and assimilation also appear in the compilations from the Food and Drug Administration.

The Panel concludes that summaries of the Poison Control Statistics and the data from the Food and Drug Administration can only be used as an indication of the potential threat posed by OTC products because ingestions of both prescription and OTC products are combined in such statistics.

REFERENCES

(1) Loew, E. R., "Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," *Annals of the New York Academy of Sciences*, 50:1142, 1950.

(2) "Poison Control Statistics, 1973," National Clearinghouse for Poison Control Centers, Bethesda, 1973.

7. *Criteria for classification of antihistamines as Category I.* In evaluating the antihistamines submitted for review, the Panel established the following criteria for classification of an ingredient as safe and effective and not misbranded for use as an antihistamine:

a. *Antihistamine activity.* If an ingredient has been tested in animal models and demonstrated to have antihistamine activity, i.e., in vitro test and in vivo tests (animal challenge with histamine and animal anaphylaxis protection), the findings were used to support a Category I determination.

b. *Animal toxicity.* If an ingredient has been tested in animals and found to have a low order of toxicity, the findings were used to support a Category I determination.

c. *Clinical studies.* If an ingredient has been tested clinically and the studies were determined to be controlled double-blind studies of an adequate design that included an appropriate dosing interval for each age group of patients, the findings were used to support a Category I determination. The Panel has discussed adequate design for clinical testing later in this document. (See part VII. paragraph C. below—Data Required for Evaluation.)

d. *Clinical experience.* If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community of safety and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that such clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. *Acceptable side effects.* If an ingredient is shown to have side effects in man for which appropriate labeling can be established, i.e., adequate directions for use and warnings against unsafe use such as "May cause drowsiness", the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse under ordinary conditions of use, could be compensated for with adequate labeling. The Panel finds that this is an

especially important consideration for recommended dosages of ingredients higher than those currently available for OTC use, e.g., chlorpheniramine 4 mg or

for ingredients previously not available for OTC use, e.g., diphenhydramine.

The Panel has summarized the findings in the following table:

Active ingredients	Antihistamine activity ¹	Animal toxicity ²	Clinical studies ³	Clinical experience ⁴	Acceptable side effects ⁵
Brompheniramine maleate.....	+	+	+	+	+
Chlorpheniramine Maleate.....	+	+	+	+	+
Diphenhydramine hydrochloride...	+	+	0	+	++
Doxylamine succinate.....	+	+	+	+	++
Methapyrillene fumarate and hydrochloride.....	+	+	0	+	++
Phenindamine tartrate.....	+	+	0	+	+-
Pheniramine maleate.....	+	+	0	+	++
Phenyltoloramine citrate.....	+	+	0	0	+
Fromethazine hydrochloride.....	+	+	0	+	++
Pyrilamine maleate.....	+	+	0	+	+-
Thenylidamine hydrochloride.....	+	+	0	0	0
Thonzylamine hydrochloride.....	+	+	0	+	+

¹ The (+) symbol indicates that the ingredient showed antihistamine activity in animals.

² The (+) symbol indicates that animal studies are available and show low toxicity.

³ The (+) symbol indicates that controlled double-blind clinical studies of adequate design are available. The (0) symbol indicates that no data are available.

⁴ The (+) symbol indicates that adequate clinical experience with the ingredient exists. The (0) symbol indicates that no data are available.

⁵ The (+) symbol indicates a positive finding of "drowsiness." The (+-) symbol indicates a positive finding of "marked drowsiness." The (-) symbol indicates a positive finding of either "drowsiness" or "nervousness and insomnia." The (0) symbol indicates that no data are available.

The Panel has determined that if four of the five criteria are satisfied (antihistamine activity, animal toxicity, clinical experience and acceptable side effects), the ingredient may be classified as Category I. The Panel has further determined that the availability of clinical studies is not always required for each ingredient. The Panel has fully discussed these ingredients in the appropriate sections below. (See part VII, paragraph B. below—Categorization of Data.)

8. *Summary.* The antihistamine ingredients as a group are strikingly antihistaminic in animal models. This is their main pharmacologic action and appears to be closely related to their clinical effectiveness. The Panel has found that three of these ingredients, chlorpheniramine, brompheniramine, and doxylamine, have been subjected to controlled clinical studies which support their clinical effectiveness. For most of the remaining ingredients marketed OTC, extensive clinical use over a period exceeding 20 years indicates that these antihistaminic drugs are also effective in treating allergic rhinitis. As a group the antihistamines possess a low order of toxicity which the Panel feels is essential for the use of any ingredient in the OTC market.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following antihistamine active ingredients as generally recognized as safe and effective and not misbranded:

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrillene preparations: Methapyrillene

fumarate, Methapyrillene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Fromethazine hydrochloride
Pyrilamine maleate
Thonzylamine hydrochloride

a. *Brompheniramine maleate.* The Panel concludes that brompheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Studies in animals indicate that brompheniramine maleate has low toxicity (Ref. 1). The chief side effect of brompheniramine, is sedation which occurs in about 20 percent or less of patients taking clinically effective doses (Refs. 2 and 3). Also observed is an atropine-like effect (anticholinergic action), which is not pronounced, but might have an adverse effect in patients with narrow angle glaucoma. The drying effect due to atropine-like action has been considered to be disadvantageous in patients with asthma because drying of secretions interferes with their removal from the airway. However, the Panel is unable to find evidence that these possible adverse effects are of clinical significance (Ref. 4).

Recovery from accidental overdosage with brompheniramine indicates that this drug has a wide margin of safety (Ref. 5). An injection of 100 mg caused only dry mouth 8 hours later in a hospitalized patient (Ref. 5). Observations in children indicate a relatively low degree of toxicity for brompheniramine (Ref. 2).

A 6-year-old boy tolerated 8 mg/lb/24 hours orally. A 2-year-old boy received a single oral dose of 60 mg without side effects and a 4-year-old boy received 96 mg in a single dose and subsequently had mild drowsiness. A 2½-year-old boy ingested an estimated twenty-five 12 mg tablets in whom hyperactivity and convulsions occurred followed by gastric lavage 2½ hours later with final recovery (Refs. 1 and 6).

The Panel is aware of a reported case of agranulocytosis following therapy with two antihistaminic drugs, thenalidine tartrate and parabromdylamine maleate (Ref. 7). The incident occurred during 1958 in which a 64-year-old female had taken both drugs. The drug manufacturer of thenalidine tartrate discontinued marketing the ingredient within months of its reported association in the medical literature with agranulocytosis. The other drug, parabromdylamine maleate, is also known as brompheniramine maleate. The patient had taken 4 mg brompheniramine maleate orally 4 times daily concurrently with an antibiotic ointment for the treatment of a pruritic rash. The patient received a total dose of 568 mg brompheniramine maleate over a period of approximately 60 days. The symptoms persisted and the drug was discontinued at which time 25 mg thenalidine tartrate was given orally 4 times daily for an additional period of approximately 60 days for a total dose of 1,850 mg thenalidine maleate prior to hospitalization. The author reporting the case noted that previous investigators had reported three cases of agranulocytosis associated with thenalidine tartrate therapy (Ref. 8). The Panel concludes that the data do not adequately substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasia. The drug has been extensively marketed and available by prescription for over 15 years with no documented cases of agranulocytosis occurring.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 600 million dosage units of brompheniramine maleate were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 568 reported cases of suspected poisonings for brompheniramine maleate, 17.1 percent exhibited some symptoms and 5.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There was one fatality reported with the drug identified as a contributing cause of death but it was not possible to determine whether the ingestion was accidental or suicidal.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 47 adverse reaction reports on three marketed products containing brompheniramine since 1968 (Ref. 9). Of the 47, no adverse reactions were listed as being definitely related to ingestion of brompheniramine, 43 were listed as probably caused by ingestion of the drug and 4 were listed as possibly related to its ingestion.

The only other serious adverse reaction, aplastic anemia, was listed as possibly related to brompheniramine ingestion. A review of the source document disclosed few details of the case except that several other drugs were also ingested. The Panel was unable to conclude from the sketchy data whether there was any relationship between ingestion of brompheniramine and the aplastic anemia.

It should be noted that while brompheniramine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that brompheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Studies in animals have shown brompheniramine to have intense antihistaminic activity and to protect against anaphylaxis (Refs. 1 and 6). In addition to its demonstrated effectiveness as an antihistamine and protection against anaphylaxis in animals, brompheniramine has been shown in double-blind studies in humans to be effective in suppressing the symptoms of allergic rhinitis in doses of 4 mg or more given at 4 to 6 hour intervals (Refs. 10 through 12).

Available evidence indicates that brompheniramine has about the same effectiveness on a mg for mg basis as chlorpheniramine (Ref. 13).

In studies of the treatment of perennial rhinitis, efficacy was reported in 23 children ages 2 months to 2 years at a dosage of 0.2 mg to 0.5 mg/lb in 24 hours divided into 3 doses (Ref. 2). Likewise, 0.2 mg/lb in 24 hours was reported as effective in 28 children ages 2 to 6 years and 0.15 mg/lb in 24 hours in 16 children ages 6 to 14 years. Most of these patients had received other antihistamines without benefit. In addition to treatment with brompheniramine, all had been instructed in environmental control measures and many were receiving injections of allergenic extracts. The contribution made by these measures to the reported benefit cannot be assessed. There were no controlled groups although the statement is made that the patients were selected by "alternate allocation," the meaning of which is unclear. The statement that over three-fourths of the patients had failed to obtain benefit from "various other antihistaminic agents" is surprising in the light of what is known today about the efficacy of the antihistaminic drugs in rhinitis. Therefore, the Panel concludes that evidence of effectiveness for children is insufficient.

The Panel concludes that brompheniramine maleate 4 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII para-

graph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: "Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours."

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- b. *Chlorpheniramine maleate.* The Panel concludes that chlorpheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.
- (1) *Safety.* The chief side effect of chlorpheniramine is sedation which occurs in about 10 to 20 percent of persons taking clinically effective doses. The drug also has a mild atropine-like effect (anticholinergic action) in some patients. This effect might have an adverse effect in patients with narrow angle glaucoma. Likewise, a drying effect has been considered to be a disadvantage in patients with asthma because drying of secretions interferes with their removal from the airways. Data supporting these potentially adverse effects in glaucoma and asthma are not available. Overdosage with chlorpheniramine has been rela-

tively well tolerated. Adults receiving 1.5 gm orally in 69 hours and 200 mg in a single intramuscular dose recovered from the induced side effects without incident (Ref. 1) as did a 4-year-old boy who received 175 mg orally in 3½ hours (Ref. 2).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 2 billion dosage units of chlorpheniramine maleate were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 1,609 reported suspected poisonings for chlorpheniramine maleate 15.8 percent exhibited some symptoms and 5.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 14 adverse reaction reports on chlorpheniramine since 1968 (Ref. 3). Of the 14 reports, no adverse reactions were listed as being definitely related to ingestion of chlorpheniramine, three were listed as probably caused by this drug's ingestion, five were listed as possibly related to its ingestion and six were listed as remotely related to ingestion of this drug.

It should be noted that chlorpheniramine is available by prescription at the 4 mg dosage level and OTC at the 2 mg dosage level. However, the safety picture presented by the prescription dosage level has given the Panel a reasonably accurate idea of what to expect from OTC marketing of the 4 mg dosage level.

The Panel concludes that chlorpheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Chlorpheniramine has been demonstrated to be effective in animal challenge tests with histamine in anaphylaxis protection (Ref. 4). In addition, its effectiveness in doses of 4 to 8 mg 4 times daily in the treatment of allergic rhinitis is described in a number of articles and uncontrolled studies and is supported by controlled studies (Refs. 5 through 8).

In a double-blind controlled study of the effectiveness of doxylamine succinate, chlorpheniramine was included as a standard of effectiveness. In this study 7.5 mg and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from 7.5 or 12.5 mg doxylamine. In this study measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 9). Other studies corroborate this finding. Using measurements of resistance to airflow in the nose, a well-controlled study

to determine the effect of chlorpheniramine given in an oral dose of 4 mg on relief of nasal obstruction gave no objective evidence of any effect over a period of 4 hours (Ref. 10). There was a significant decrease in resistance to flow when pseudoephedrine was given in a dose of 30 mg, indicating that the method was capable of revealing therapeutic effect. Likewise, a study submitted in an OTC Volume showed increased nasal obstruction in patients with nonallergic acute rhinitis after 8 mg chlorpheniramine in sustained action form (Ref. 11). Both of these studies were done in patients without evidence of allergy. These studies indicate that chlorpheniramine does not relieve and indeed, may aggravate nasal obstruction.

Only one study (Ref. 5) appears to have been done using a 2 mg dose, which is commonly used in OTC preparations, demonstrating effectiveness. The Panel concludes that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg.

The Panel concludes that chlorpheniramine maleate 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine has a low order of toxicity in laboratory animals (Ref. 1). Its first clinical use was in 1946. Since then it has been used widely for treatment of such common conditions as allergic rhinitis, sundry rashes, the "common cold", and has also been used as a sedative. With the exception of sedation, adverse effects have been rare and the drug is considered safe. The Panel has also reviewed the side effects and toxicity of diphenhydramine when used as an antitussive and finds it to be safe when used at the same dosage level and regimen. That safety discussion is included elsewhere in this document. See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

In a double-blind study in 20 males (Ref. 2) there was no evidence of interference with tests for memory, rotary pursuit, or reaction time at a dose of 12.5 mg or 25 mg. These doses are below that recommended for adults on the treatment of allergic rhinitis. Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Refs. 3 and 4). In some individuals, this occurs to a degree which would probably impair competence in driving a car or operating machinery. An atropine-like effect is also frequently described by patients as a drying sensation of the mouth and nose.

Many toxicologic studies have been carried out on diphenhydramine hydrochloride. Unpublished animal studies performed with mice demonstrated the LD₅₀ to be 145 mg/kg and 263.0 mg/kg (Refs. 5 through 7). In rats, the LD₅₀ was found to be 520 mg/kg and 549.5 mg/kg. The results of these studies are very similar when different animal strains, times when the studies were run, and variations inherent under different laboratory conditions are considered (Ref. 5). Diphenhydramine hydrochloride was demonstrated to have low toxicity in all three studies. Based upon these studies the usual adult human oral dosage level of 50 mg or 0.7 mg/kg 3 to 4 times daily is 1/200th of the oral LD₅₀ of diphenhydramine hydrochloride in mice (the LD₅₀ is equivalent to at least 200 times the therapeutic dose in man) and 1/400th the LD₅₀ in rats (the LD₅₀ is equivalent to at least 700 times the therapeutic dose in man) (Ref. 5).

In chronic toxicity studies dogs were given diphenhydramine hydrochloride at dosage levels of 10, 25, 40 and 60 mg/kg/day for periods up to 6 months. There were no gross microscopic pathologic changes attributable to diphenhydramine hydrochloride (Ref. 5).

Toxic psychoses from overdoses of diphenhydramine have occurred. A case of schizophrenic-like behavior was de-

scribed by Nigro (Ref. 8). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 9).

Wynngaarden and Seevers also found that very high doses of diphenhydramine in infants may cause excitement and convulsions. They reviewed three cases in children under 3 years of age (2½, 1½, and 1½ years of age) who had taken 850 mg, 800 mg and 150 to 250 mg of diphenhydramine respectively with all doses resulting in convulsions (Ref. 10). In another case, a 32-month-old baby swallowed 9 capsules (450 mg) of diphenhydramine, after which a state of excitation was observed. Phenobarbital was prescribed, and the next day, the baby was normal (Ref. 10).

They also reviewed a group of adults ranging from 18 to 72 years, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal, or somnolence (Ref. 10).

One case involved a 72-year-old asthmatic man, weighing 145 pounds who ingested 2,500 mg (50 capsules) of diphenhydramine hydrochloride. He fell into a deep sleep. Approximately 16 hours later, he awoke, feeling well. He had received no medication for this somnolence. In other cases dealing with adult fatalities, Wynngaarden and Seevers found that the ability to withstand large overdoses appears to increase with age, and the older the patient, the more the toxic manifestation shifts from that of central nervous system stimulation to that of depression. But it was also seen that a 47-year-old severely asthmatic woman died in depression after ingesting only 200 mg of diphenhydramine hydrochloride. However, the death cannot be unequivocally attributed to diphenhydramine since the shock-like state observed could well have been a complication of the disease itself and could easily have been influenced by other depressant medicaments that were given (Ref. 9).

The Panel considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 187.4 million dosage units of diphenhydramine hydrochloride were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 334 reported suspected poisonings for diphenhydramine hydrochloride, 37.4 percent exhibited some symptoms and 16.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were two fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 178 adverse reaction reports on diphenhydramine since 1968 (Ref. 11). Of those 178 reports, nine were listed as definitely related to diphenhydramine ingestion, 95 were listed as probably caused by the drug's ingestion, 58 were listed as possibly related to its ingestion and 16 were listed as remotely related to diphenhydramine ingestion.

A 69-year-old female who had a history of serious medical problems and

drug ingestion was diagnosed to have agranulocytosis. Three days after termination of pentazocine lactate by injection and 1 day after termination of diphenhydramine therapy, her white blood cell count progressively climbed to normal values (Ref. 11).

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel notes that the dosage levels of diphenhydramine currently available by prescription are comparable to those that would be available for OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal tests, diphenhydramine has an intense antihistamine-action both in vitro (Refs. 1 and 12) and in vivo (Refs. 1 and 13). The drug gives protection to guinea pigs against anaphylactic shock (Ref. 13).

Diphenhydramine is also effective for the symptomatic treatment of allergic rhinitis. Although no studies with a double-blind control were found, the Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on wide usage over a period of 30 years.

A number of uncontrolled clinical studies indicate that the drug is effective in relieving the symptoms of allergic

rhinitis (Refs. 14 through 16) and one study also describes reduction of whealing in the skin induced by intracutaneous injection of both histamine and allergic extracts in patients with hay fever (Ref. 17). The Panel has also found the drug to be effective for use as an antitussive, which is discussed elsewhere in this document. (See part III paragraph B.1.c. above—Diphenhydramine hydrochloride.)

The Panel concludes that diphenhydramine hydrochloride 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistaminic active ingredients. (See part VII paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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d. *Doxylamine Succinate.* The Panel concludes that doxylamine succinate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Doxylamine has a low oral toxicity in laboratory animals (LD₅₀: mice 470 mg/kg; rabbits 250 mg/kg) at doses which greatly exceed those required to demonstrate antihistaminic effects (Ref. 1). Brown and Werner found the intravenous LD₅₀ to be 49 and 62 mg/kg for rabbits and mice, respectively (Ref. 1). The subcutaneous dose in mice was about 87 percent less toxic than when given intravenously. The oral dose was about 80 percent less toxic than when given in rabbits. The administration of doses of doxylamine succinate as high as 45 mg/kg twice daily for a period of 38 days had no significant effect in rats. Repeated administration of increasing doses from 50 to 150 mg/kg also had no gross effects. However, an increase to 200 mg/kg resulted in a decreased rate of growth in some animals, and an increase up to 400 mg/kg caused lack of appetite and death in one case. Thus, repeated doses resulted in toxicity only when the doses approached acutely lethal ones (Ref. 1). Daily administration of doxylamine to dogs, rats and monkeys in doses of 3 to 7.5 mg/kg for 2 months gave no evidence of accumulation and the drug was well tolerated (Ref. 2).

Clinical experience indicates that the primary side effect in humans is central nervous system depression. Standard scientific tests state that there is a high incidence of sedation at the usual therapeutic dosage of 12.5 to 25 mg up to 4 times daily (Refs. 3 through 7). In one double-blind, placebo controlled study, the hypnotic effectiveness of doxylamine, 25 to 50 mg, was greater than that of 100 mg secobarbital (Ref. 8). Dizziness and nervousness occur less frequently than sedation (Ref. 3).

One study reports that of 118 patients being treated for allergy with doses of

12.5 to 50 mg of doxylamine succinate, side effects were observed in 39 (Ref. 9). Sedation or sleepiness was seen in 36 of these 39 patients or 92 percent. Nervousness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months. Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 50 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, there was no apparent correlation, they stated, between the dosage of the drug and drowsiness. Palpitation, irritability, and diarrhea were noted in three patients. There was no evidence of any hepatic, renal or vascular changes. In the study by Ferguson there was no change in pulse, respiration, temperature or blood pressure with high doses of up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months (Ref. 11). Blood chemistry and organ function tests remained normal. In addition, Ferguson found that there has been no habituation to doxylamine, but he noted a mild degree of tolerance (Ref. 11).

Selzer and Waldman gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months in which side effects were virtually nonexistent (Ref. 12).

In a review of antihistaminic drugs, it is reported that 36 percent of 56 patients receiving the drug for treatment of allergic rhinitis had side effects, chiefly drowsiness (Ref. 13).

It appears from some studies that 50 mg and above of doxylamine succinate produces the side effect of sedation which is characteristic of antihistamines (Refs. 9 and 13). However, as stated above, Ferguson (Ref. 11) and Selzer and Waldman (Ref. 12) gave doses up to 900 mg daily in three divided doses with little evidence of drowsiness in the schizophrenic patients. Such apparently contradictory results have not yet been explained.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 60 million dosage units of doxylamine succinate were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 100 suspected poisonings reported for doxylamine succinate, 32 percent exhibited some symptoms and 5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel has reviewed and concurs with the statement in the report of the Advisory Review Panel on OTC Sedatives, Tranquillizers and Sleep-Aid Drug Products published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) "that no literature was found by the Panel concerning poisoning or doses which cause death in humans."

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 10 adverse reaction reports on doxylamine succinate since 1968 (Ref. 14). Of the 10 reports none was listed as directly related to ingestion of doxylamine succinate, five were

listed as probably caused by this drug's ingestion, three were listed as possibly related to its ingestion and two were listed as remotely related to ingestion of doxylamine succinate.

The Panel concludes that doxylamine succinate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Doxylamine is highly active in the protection of guinea pigs against the intravenous injection of histamine (Ref. 1). Using ileum strips in vitro, marked antihistaminic action was also demonstrated. The drug was also effective in protecting guinea pigs against anaphylaxis (Ref. 1).

Clinical experience and standard scientific textbooks indicate that doxylamine is an effective antihistamine in dosages of 12.5 to 25 mg up to 4 times daily (Refs. 3, 7, and 15).

Two double-blind clinical trials have demonstrated the effectiveness of doxylamine in a dosage of 12.5 and 25 mg up to 4 times daily in the treatment of hay fever (Refs. 15 and 16). In these studies, subjective evaluations by patients and physicians were logged and analyzed.

In a third well-designed study, doxylamine was given in a dose of 7.5 mg to one group and in a dose of 12.5 mg to a second group and a placebo to a third group, all with allergic rhinitis caused by pollen. The preparations were administered 4 times a day as required for 6 days with double-blind control. There were 40 to 45 patients in each group. Both the 7.5 mg and 12.5 mg dosages gave significant relief of symptoms as compared with the placebo, with the effectiveness of 12.5 mg exceeding that of 7.5 mg (Ref. 17). The incidence of drowsiness in both the 7.5 mg and 12.5 mg groups was not different from placebo.

In a fourth well-designed study with double-blind control, 7.5 and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from either 7.5 or 12.5 mg doxylamine. In this study, measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 17). One study ranked doxylamine 8th in a series of 13 antihistamines tested for antihistamine activity in man (histamine wheal test) (Ref. 18). Doxylamine has also been described as being slightly "less potent" than promethazine but having a longer duration of action (Ref. 5). An effective dosage for children 6 to 12 years of age is 6.25 mg 2 to 4 times daily (Ref. 3) or 2 mg/kg/24 hours of 60 mg/m²/24 hours divided in 4 to 6 doses (Ref. 19).

The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (1) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

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e. *Methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride)*. The Panel concludes that methapyrilene fumarate and methapyrilene hydrochloride are safe and effective for OTC use as antihistamines in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety*. In animal studies, methapyrilene appears to have a low order of toxicity in laboratory animals as compared with other common antihistaminics (Refs. 1 and 2). From the results of human studies, methapyrilene appears to be safe at the recommended dosage (Ref. 3). Specifically, in the Friedlaender and Friedlaender study (Ref. 4) of 117 patients, one or more side effects, usually mild in nature, were encountered in approximately 25 percent of the patients receiving methapyrilene hydrochloride. These occurred most often when doses of 100 mg were administered but usually abated after the initial treatment and seldom affected the continued use of the drug. In most instances, a reduction in dosage to 50 mg obviated the side effects while not modifying the effectiveness. Drowsiness, the most common side effect, occurred in 13 patients. Vertigo, headache, nausea and vomiting, diarrhea, excessive dryness of mouth were not in order of frequency. No serious toxic effect was observed in any patients in this group receiving a daily dose of 200 to 300 mg (50 mg every 4 to 6 hours) (Ref. 4).

In another study, Peirce and Mothersill studied 77 patients and reported that five patients who had been treated with methapyrilene hydrochloride in daily amounts of 100 to 200 mg showed minor side effects but no toxic symptoms (Ref. 5). Rarely did side effects interfere with the patient's ability to continue the administration of the drug. In some cases, lowering the dosage obviated the side effects without significantly altering the therapeutic effectiveness of the drug. Peirce and Mothersill concluded that, ordinarily, 200 mg could be taken daily with "no discomfort" (Ref. 5).

Douglas stated that methapyrilene hydrochloride has been found to have low to intermediate activity for sedation, and its action is less pronounced than that of other antihistamines in therapeutic doses, particularly diphenhydramine (Ref. 3). Occasionally, the anticholinergic action of antihistamines generally may predominate and methapyrilene may cause excitation that results in insomnia, tremors, nervousness, irritability, and palpitation. Dryness of mouth, blurred vision, urinary retention, tachycardia, and constipation may also occur, but these reactions are rare unless large doses are used (Ref. 3). This same view

of the toxicity of methapyrilene also appears in several other standard scientific texts (AMA Drug Evaluation, and New and Nonofficial Drugs) (Refs. 6 and 7). However, AMA Drug Evaluation also states that convulsions have been reported in patients with focal lesions of the cerebral cortex and in individuals who have ingested toxic doses (Refs. 6 and 7).

In a study of three patients receiving 400 mg a day for 8 to 10 weeks, no change in blood or urine constituents was observed (Ref. 4). An accidental overdose of 800 mg methapyrilene in a 20-month-old infant resulted in cyanosis, loss of consciousness, convulsions, and cardio-respiratory depression with eventual recovery (Ref. 8). An unusual case of fever, rigor, vomiting, and general malaise with recovery after 3 days is also described (Ref. 9). The symptoms recurred after challenge with methapyrilene 2 weeks after the initial attack. An 18-year-old man who became stuporous after ingestion of an unknown quantity of methapyrilene recovered (Ref. 10).

Methapyrilene fatalities have included a 16-month-old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 11), an adult suicide who died in convulsions after ingestion of methapyrilene (Ref. 12), and two other adults who were found dead (Refs. 13 and 14). Nonfatal cases include two adults (Ref. 15) manifesting convulsions, and two other adults in coma (Ref. 16).

The panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 543 million dosage units of methapyrilene were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 168 suspected poisonings reported for methapyrilene fumarate or methapyrilene hydrochloride, 11.9 percent exhibited some symptoms and 5.9 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of one adverse reaction report on methapyrilene since 1968 (Ref. 17).

The Panel concludes that methapyrilene fumarate and methapyrilene hydrochloride are safe for OTC use as antihistamines in the dosage ranges described below.

(2) *Effectiveness*. Tests in animal models have demonstrated methapyrilene's specific antihistamine activity. Methapyrilene prevents histamine-induced contraction of the guinea pig ileum and protects sensitized guinea pigs from anaphylactic shock when challenged with an antigen (Refs. 2 and 18).

No double-blind human studies using methapyrilene alone were found. Uncontrolled studies of methapyrilene reported that 63 to 79 percent of patients suffering from hives or hay fever were relieved following administration of the drug (Refs. 4, 5, 15, 18, and 19). In the Friedlaender study, approximately 75 percent of the

40 patients suffering from acute seasonal hay fever obtained some benefit from methapyrilene fumarate or methapyrilene hydrochloride, although the relief of the symptoms was seldom complete. This study utilized 100 mg doses in adults, administered 4 times daily, after meals and at bedtime (Ref. 20).

The Peirce and Mothersill study found that 75 patients received methapyrilene hydrochloride for periods varying from 1 day to 3 months (Ref. 5). The medication exhibited its greatest effectiveness in acute skin rash due to drug and food allergy, watery eyes and runny nose due to pollen sensitivity, and histamine induced headaches. They found that the effective dosage ranged from 50 to 400 mg daily. The average maintenance dose for all cases was between 150 to 200 mg daily (Ref. 5).

In the Feinberg and Bernstein study of 112 patients with allergic rhinitis (seasonal as well as that due to the pollen of trees, grasses and weeds, and to the spores of molds), 79 patients or 70 percent benefited from methapyrilene hydrochloride. Of 95 patients with vasomotor rhinitis (nonseasonal hay fever) 44 patients or 46 percent received some measure of relief (Ref. 19). The symptoms of asthma were not appreciably altered in 30 patients although the preasthmatic, spasmodic cough was decidedly helped in 6 out of 9 patients. The subjective symptoms of skin rash were helped in 4 of 12 patients. In 13 patients with atopic dermatitis (skin rash), 8 obtained considerable relief from itching. The average dose of methapyrilene hydrochloride in the Feinberg-Bernstein study was 50 mg orally, 1 to 4 times daily (Ref. 19). A controlled study of 236 patients receiving methapyrilene and 203 receiving powdered starch presented no evidence that methapyrilene aborted or ameliorated colds (Ref. 20).

The Panel concludes that methapyrilene fumarate 50 mg and methapyrilene hydrochloride 50 mg are the minimum effective OTC dosages for the relief of the symptoms of allergic rhinitis.

(3) *Dosage*. Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (1) *Warning*. "May cause marked drowsiness."

(ii) *Professional labeling*. The Panel recommends that labeling provided to health professionals, but not to the general public may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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1. *Phenindamine tartrate*. The Panel concludes that phenindamine tartrate is safe and effective for OTC use as an antihistamine in suppressing the symptoms

of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety*. Acute toxicity studies in guinea pigs indicated an LD₅₀ value of 125 mg intraperitoneally which is approximately the same as the intraperitoneal LD₅₀ value for diphenhydramine. Daily doses of 100 mg for 5 months or of 200 mg for 6 months were reported to have no adverse effects on the weight, blood formation, blood glucose and non protein nitrogen of dogs. No histopathological changes were found (Refs. 1 and 2).

In 136 healthy subjects ingesting 75 to 600 mg phenindamine daily for 7 to 31 days, toxicity studies revealed no abnormality of hemoglobin, red cell count or white cell count, urinalysis, blood pressure, electrocardiogram, gastric acidity, glucose tolerance, pulse rate, basal metabolic rate or blood chemistry (Ref. 3). In 15 healthy volunteers receiving 50 mg or more daily for 6 months, the blood and urine remained normal (Ref. 4).

In 280 patients receiving 25 to 150 mg daily (adults averaging 75 mg; children 30 mg daily), there were side effects in 27 percent (Ref. 1). In more than 1,000 subjects side effects were frequent but mild and were directly related to dosage. At 75 mg daily, 15 percent of the subjects developed side effects. At 150 mg daily, 25 percent of 380 patients developed side effects. At 300 mg daily, 50 percent of the patients suffered side reactions, and many discontinued the drug. Receiving a dose of 600 mg daily for 7 days, 75 percent of the patients developed side effects (Refs. 3 and 5). Side effects included insomnia, stimulation, nervousness, dryness of mouth, and drowsiness (Refs. 1 through 6).

The Panel recognizes that phenindamine may produce stimulation in some persons and drowsiness in others (Ref. 7). In one study, stimulation is reported to have occurred in 35 percent of patients (Ref. 4). In a review of clinical studies (Ref. 7) comprising 250 patients with allergic rhinitis, it was reported that 3 percent had drowsiness and 12 percent had stimulation. However, 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.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 14 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 118 reported suspected poisonings for phenindamine tartrate, 21.2 percent exhibited some symptoms and 10.2 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on phenindamine tartrate since 1968 (Ref. 8).

The Panel concludes that phenindamine tartrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness*. The Panel concludes on the basis of clinical reports that phenindamine tartrate is effective for OTC use in the treatment of the symptoms of allergic rhinitis (Refs. 2, 3 and 6).

Phenindamine tartrate demonstrated antihistaminic activity in animals. It could protect guinea pigs against lethal doses of histamine. The histamine-induced contraction of guinea pig intestinal strips in vitro was inhibited by phenindamine. The drug also had a protective action in guinea pigs against fatal anaphylactic shock produced by horse serum sensitization (Refs. 1 and 2).

Clinical trials have also shown the effectiveness of phenindamine tartrate as an antihistamine in man. A dose of 200 mg of phenindamine inhibited the wheals and flares produced in ragweed-sensitive patients after they were skintested with ragweed or histamine (Ref. 2).

In a subjective, uncontrolled clinical evaluation of phenindamine in 389 patients with allergic conditions such as hay fever, allergic perennial rhinitis, bronchial asthma, atopic dermatitis, contact dermatitis, urticaria and angioneurotic edema, and migraine, a dose of 25 mg every 4 hours was given orally (Ref. 2). Of the 180 patients in the study with hay fever who took the drug during the hay fever season, 44 percent reported complete relief, 32 percent reported moderate relief, 14 percent had slight relief and 10 percent reported no relief. In the 71 patients with allergic perennial rhinitis, 35 percent had complete relief, 39 percent moderate relief, 9 percent slight relief and 17 percent had no relief. The relief from a dose of 25 mg lasted approximately 2 to 5 hours. Of the 389 patients, 23 percent had side reactions such as nervousness, palpitations, nausea, vomiting, insomnia, drowsiness, headache, constipation, etc. No appreciable change was seen in blood pressure or electrocardiogram.

In another report, 78.2 percent of 197 patients with hay fever who were given a daily dose of 25 to 150 mg of phenindamine for an average of 17 days reported fair to excellent relief (Ref. 1). The drug was of benefit to 76.1 percent of the 71 patients with nonseasonal vasomotor rhinitis in this study.

The symptomatic relief of allergic rhinitis by daily doses of 25 to 200 mg of phenindamine was studied in 131 patients. Seventy-five to 100 percent relief was reported by 105 of these patients whose ages ranged from 2 to 70 years. Only 27 of the patients complained of side effects (Ref. 6). In a study of 40 patients with hay fever, a daily dose of 25 to 75 mg gave marked relief to 52.5 percent, moderate relief to 25 percent, slight relief to 15 percent and 7.5 percent had no relief (Ref. 4). Daily doses of 75 to 120 mg phenindamine for 15 to 120 days to 66 hay fever subjects gave complete

relief to 18 percent, partial relief to 62 percent and 20 percent were not helped (Ref. 3). Daily doses of 75 to 250 mg to 25 patients with vasomotor rhinitis brought no relief for 44 percent and complete relief for 20 percent. At 75 mg daily, approximately 15 percent of the patients showed side effects.

Experience has also indicated that the duration of effect of one 25 mg dose is 2 to 10 hours averaging 4 to 5 hours. The onset of action is rapid, occurring within 15 minutes of ingestion (Ref. 1). In one study, 86 percent of 66 patients with hay fever received moderate to complete relief receiving a dosage of 75 to 150 mg daily. In a review of the antihistamine drugs (Ref. 7), 76 percent of 912 patients with allergic rhinitis were benefited.

In one study, moderate to marked relief of hay fever occurred in 78 percent of 40 patients taking 50 mg daily (Ref. 4).

Seventy-eight percent of patients with hay fever noted fair to excellent relief (Ref. 1). A placebo failed to provide relief of the symptoms in these patients.

The Panel concludes that pheniramine tartrate 25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See Part VII, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Caution: May cause nervousness and insomnia in some individuals."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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(8) OTC Volume 040325.

g. Pheniramine maleate. The Panel concludes that pheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity and a low order of toxicity (Refs. 1 and 2). Clinical experience has confirmed that pheniramine maleate is safe in the dosage ranges used as an antihistamine. The chief side effect of pheniramine appears to be sedation. It also appears to have a mild atropine-like effect. Since most of the studies have been done with other drugs combined with pheniramine, the action of this drug alone cannot be described with certainty. In one study in which pheniramine alone was given, drowsiness and dryness of the mouth (atropine-like effect) occurred in 11 percent of the subjects (Ref. 3). In a review of clinical studies with the antihistamine drugs (Ref. 4) 29 percent of 49 patients receiving pheniramine maleate 25 mg for allergic rhinitis had side effects, chiefly drowsiness. Among 184 subjects receiving 10 mg pheniramine 4 times daily in the course of a double-blind study of the "common cold," side effects, chiefly drowsiness, did not significantly exceed the side effects in an equal number of subjects receiving a placebo (Ref. 5). There appear to be no reports of accidental overdose. A single case was described in which acute psychosis occurred following treatment for 2 months with pheniramine 25 mg 3 times daily (Ref. 6). Following withdrawal of pheniramine, recovery occurred in 8 days. No definite conclusion could be drawn in this case as to the role played by pheniramine. An atropine-like effect suggests a potential hazard in patients with enlargement of the prostate gland and also narrow angle glaucoma and this effect has also been considered to be disadvantageous in patients with asthma although data supporting this potentially adverse effect are not available.

The Panel has considered the most recent data available from the records compiled from Poison-Control Centers during 1973 in which a minimum of 291 million dosage units were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pheniramine maleate, 20 percent exhibited some symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on pheniramine maleate since 1968 (Ref. 7).

The Panel concludes that pheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity (Refs. 1 and 2).

There are no well-controlled studies documenting the effectiveness of pheniramine maleate as an antihistamine. In a review of several reports of clinical experience, pheniramine in a dose of 25 mg gave relief of allergic rhinitis in 81 percent of 442 patients (Ref. 4). Likewise the drug gave relief in 66 percent of patients with nonallergic rhinitis (vasomotor rhinitis).

The Panel concludes that pheniramine maleate 12.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg every 4 or 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public), may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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- (5) Lowell, P. C. et al., "The Antihistaminic Drugs in the Treatment of the Common Cold," *New England Journal of Medicine*, 244:132, 1951.
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(7) OTC Volume 040325.

h. Promethazine hydrochloride. The Panel concludes that promethazine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) **Safety.** Promethazine is well-tolerated by laboratory animals; doses which greatly exceed those giving protection against histamine are well tolerated by guinea pigs (Ref. 1). Like other antihistamine drugs, promethazine may cause drowsiness when taken in clinically effective doses. In a study in which up to 1 gm was administered therapeutically 4 times daily to psychiatric patients, drowsiness occurred as the most important and frequent side effect (Ref. 2). In a suicide attempt a 35-year-old female survived an estimated dose of 1.5 gm, developing coma and clonic contractions (Ref. 3). Another such case had a similar course after the patient consumed 500 mg of promethazine (Ref. 4). Children may be less tolerant of this drug. Seven to 10 hours after a 12-year-old boy ingested 200 mg, he was hospitalized with many symptoms including restlessness, excitation, stupor, fright and hallucinations. Recovery followed in 3 days (Ref. 5).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 385 million dosage units were sold. (See part VII paragraph A.6. above—Human toxicity.) Of the 56 reported suspected poisonings for promethazine, 28.6 percent exhibited some symptoms and 14.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug. This relative incidence of adverse reactions is remarkably low in light of the substantial and long use of the drug (4½ billion oral doses have been used since 1951 (Ref. 6)).

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 169 adverse reactions involving marketed products containing promethazine (Ref. 7). Of the 169, 4 adverse reactions were listed as being definitely related to the oral ingestion or injection of promethazine, 105 were listed as probably caused by the drug's use, 49 were listed as possibly related to its use and 11 were listed as remotely related to promethazine.

Of particular concern are blood dyscrasias which have been reportedly associated with the drug. A total of five adverse experience reports have remotely related blood dyscrasias to promethazine. Analysis of the experience reports indicates that these dyscrasias are not attributable to promethazine. One case of agranulocytosis is reported to have occurred in a patient who was receiving promethazine and methaqualone. The patient's white blood cell count and the neutrophils began to increase and returned to normal 3 days after methaqualone was discontinued. Agra-

nulocytosis was reported in another patient receiving large doses of two antibiotics intravenously who was also receiving oral promethazine. Additional drugs in the regimen included a thyroid derivative and tetracycline prior to the other medications. This blood dyscrasia may well be attributed to the two antibiotics, methacillin and/or cephalothin, both of which are known to cause agranulocytosis. A case of thrombocytopenia was reported in a 2-year-old child who developed symptoms of an upper respiratory infection with fever and cough. The patient was treated with aspirin, a product containing triprolidine hydrochloride and pseudoephedrine, and promethazine syrup with dextromethorphan. The attending physician believed that the thrombocytopenia was caused by the basic disease process and not by the medications. Leukopenia and thrombocytopenia was reported in a patient receiving promethazine but there are no data provided on the patient's disease state or concomitant drug therapy. On the basis of this limited data it is not possible to determine the cause and effect relationship between promethazine and the blood dyscrasias. Another patient, an 88-year-old male, with an upper respiratory infection who was receiving promethazine, tetracycline and propoxyphene reportedly had hypoplastic anemia secondary to drug reaction. Again, no information on drug dosages or final diagnosis was available and promethazine cannot be determined to cause the hypoplastic anemia.

A further review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program and the University of Florida adverse reaction study shows a low incidence (5.2 percent and 7.1 percent, respectively) of adverse reactions (Ref. 8). The most frequently occurring reactions were drowsiness and confusion or disorientation. In contrast to other phenothiazine derivatives, promethazine showed few incidences of extrapyramidal syndrome (1 of 2,468 patients followed in the studies who received promethazine) and hypotension (3 of 2,468 patients followed in the studies who received promethazine).

Clinical studies (Refs. 1, 9, 10, and 11) indicate that the drug is safe in a dosage effective in allergic rhinitis and authorities in the field of clinical allergy concur (Refs. 12 and 13).

The Panel is aware of the current package insert labeling for promethazine which warns against various possible adverse reactions. These adverse effects are those usually associated with phenothiazine derivatives and clinical experience generally supports their occurrence with most other phenothiazine compounds. According to one authority, jaundice, excessive hypotension or hematopoietic damage have not been reported (Ref. 13). After analysis of published research studies and adverse experience reports on promethazine, however, the Panel concluded that promethazine does not cause the wide range of serious or potentially toxic effects

characterizing other members of the chemical class of phenothiazines.

It should be noted that while promethazine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that promethazine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) **Effectiveness.** In animal studies, promethazine is highly effective in protecting guinea pigs against histamine and the drug is also effective in protecting guinea pigs against anaphylaxis (Ref. 13). Promethazine appears to share with other antihistamine drugs the capacity to suppress rhinorrhea, sneezing and itching but differs from most other antihistamine drugs under consideration in having a longer duration of action. However, no controlled clinical trials appear to have been done to test the effectiveness of promethazine in allergic rhinitis nor in the "common cold". A number of uncontrolled studies indicate that promethazine is effective in the treatment of allergic rhinitis in a dose of 12.5 to 25 mg (Refs. 1, 7, 10, and 13). Based on clinical experience and the data available, the Panel concludes that promethazine is effective when taken in the recommended dosage.

The Panel concludes that promethazine hydrochloride 6.25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) **Dosage.** Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) **Warning.** "May cause marked drowsiness."

(ii) **Professional labeling.** The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

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1. Pylramine maleate. The Panel concludes that pylramine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) **Safety.** Chronic animal toxicity studies done by Winter et al. showed no evidence of a cumulative effect (Ref. 1). In that study, pylramine maleate had been administered to rats, dogs and monkeys for varying lengths of time up to 6 months. The following doses appeared to be entirely safe: in rats 10 mg/kg 5 times weekly for 6 months and up to 200 mg/kg daily for 32 days; in dogs, 20 mg/kg 5 times weekly for 6 months, and in monkeys, 50 mg/kg daily for 35 days. No toxic signs nor any hematological, biochemical or pathological abnormalities were found in the animals on these doses.

In human studies, pylramine has a low order of toxicity. Side effects are not infrequent but are usually mild. They include drowsiness, listlessness, irritability, and anorexia (loss of appetite) (Ref. 2). In a study by Gay et al., only 3 percent of the 147 patients showed any sign of drowsiness and the incidence of loss of appetite, nausea and vomiting occurred in 27 percent of the patients (Ref. 3).

Two fatalities were reported with pylramine maleate. One was of a 21-month-old child who had ingested 600 mg and died 2 3/4 hours after ingestion, exhibiting a post-convulsive coma. The other fatality was of a 2-year-old child that had ingested 1,400 mg and died during convulsions 4 hours after ingestion (Ref. 4).

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of two adverse reaction reports on pylramine since 1968

(Ref. 5). Both of the adverse reactions were minor and neither was listed as directly related or probably caused by the ingestion of pylramine.

The Panel has also considered the most recent data available from the records compiled from Poison Control Centers. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pylramine maleate, 18.7 percent exhibited symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of only two adverse reaction reports on pylramine since 1968 (Ref. 5). Of the two reports, no adverse reactions were listed as being definitely related to ingestion of pylramine; both were listed as possibly related to its ingestion.

The Panel concludes that pylramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) **Effectiveness.** In vitro and in vivo animal studies indicate that pylramine has an intense antihistamine action (Ref. 6) and that the drug has protective activity against histamine and anaphylaxis in the guinea pig (Ref. 7). Pylramine and diphenhydramine were equally effective in protecting against anaphylaxis and in preventing histamine-induced contractions of sensitized guinea pig ileum. Winter found in his animal studies that 0.01 mg/kg of pylramine protected 100 percent of 19 guinea pigs against a lethal dose of histamine (0.5 mg/kg) for 2 hours (Ref. 1). Gay et al. used the same dose and 91 percent of the guinea pigs were protected for 2 hours (Ref. 3). In this same study, 80 percent of 10 guinea pigs pretreated with 0.1 mg/kg of pylramine survived. The pharmacological effects and the histamine antagonism of pylramine are comparable to those of chlorpheniramine and similar to those of the other antihistamines (Refs. 1, 6, and 7).

In an uncontrolled study of several antihistaminic drugs including pylramine (Ref. 3), this drug was given to 102 patients with allergic rhinitis of whom 70 percent were improved. Two other comparative uncontrolled studies gave similar findings (Refs. 8 and 9) and in a review of the antihistaminic drugs, 66 percent of 604 patients with allergic rhinitis usually receiving a dose of 50 mg were benefited (Ref. 10).

The Panel concludes that pylramine maleate 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) **Dosage:** Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years,

there is no recommended dosage except under the advice and supervision of a physician.

(4) **Labeling.** The Panel recommends the Category I labeling for antihistamines. (See part VII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: **Professional labeling:** The Panel recommends that the labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

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J. Thonzylamine hydrochloride. The Panel concludes that thonzylamine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) **Safety.** Thonzylamine hydrochloride has been shown in animal experiments to possess antihistaminic activity and a low order of toxicity (Ref. 1). Clinical experience has confirmed that thonzylamine hydrochloride is safe in the dosage ranges used as an antihistamine. Although there are no controlled studies using thonzylamine, the incidence and degree of side effects appear to be less than with most other antihistamines (Refs. 2 and 3). In one report in which patients with "allergies" received an average dose of 50 to 100 mg orally 2 to 4 times daily, investigators in seven separate studies concurred that

thonzylamine was the "least toxic" of the antihistamines then in general use (Ref. 4). In other studies, the incidence of side effects was also low (Refs. 5 through 9) but the dosage of thonzylamine was generally not specified. Of the entire series of 874 patients, an average of 10.9 percent reported side effects which consisted of slight nervousness, headache, gastric disturbance, drowsiness, and dizziness. Most of these side effects were not significant, but the drug was discontinued in a small number of patients due to headache or gastric disturbance.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 80 million dosage units were sold. (See part VII, paragraph A.6. above—Human toxicity.) There were no reported suspected poisonings for thonzylamine hydrochloride.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thonzylamine hydrochloride since 1968 (Ref. 10).

The Panel concludes that thonzylamine hydrochloride is safe for OTC use as an antihistamine at the dosage ranges described below.

(2) *Effectiveness.* Thonzylamine hydrochloride, administered orally, is generally recognized as possessing antihistamine properties and providing symptomatic relief in allergic rhinitis. However, there are only uncontrolled studies documenting the effectiveness of thonzylamine hydrochloride as an antihistamine.

Most textbooks and several studies (Refs. 5, 7, and 9) indicate thonzylamine hydrochloride has antihistamine action. In a series of uncontrolled studies, 64 percent of patients with "allergy" benefited from oral doses of 50 to 100 mg thonzylamine hydrochloride 2 to 4 times daily (Ref. 4) while in the other studies, thonzylamine was found to be about as effective as other antihistamine drugs. In a review of the antihistamines, thonzylamine 50 mg was reported to have given benefit in 54 percent of 384 patients with allergic rhinitis (Ref. 11). The studies cited suggest that a recommended dosage of 50 to 100 mg up to 4 times a day is effective.

The Panel concludes that thonzylamine hydrochloride 50 to 100 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I Labeling for antihistamine active ingredients. (See part VII, paragraph B.1. below—Category I Label-

ing.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antihistamine active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

b. *Warnings.* The drowsiness often produced by the antihistaminic drugs is a

potential hazard under circumstances in which alertness is important. Therefore the Panel believes that a warning regarding drowsiness should appear on the label for all products containing antihistamine drugs. The Panel believes it is prudent to regard the atropine-like effects of the antihistamines as a possible hazard in patients with glaucoma and as possibly leading to difficulty in urination in those individuals with prostatic hypertrophy. In asthma, the antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

Therefore, the Panel recommends that labeling include the following warnings and cautions: (1) For active ingredients not containing the specific warning "May cause marked drowsiness", the statement "May cause drowsiness" should be used.

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

(3) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Caution. Avoid driving a motor vehicle or operating heavy machinery".

(5) "Caution. Avoid alcoholic beverages while taking this product".

(6) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

There are insufficient data to establish the safety of OTC preparations containing antihistamines in children under 6 years. Individuals vary widely in the degree to which drowsiness, and less commonly, other adverse effects occur when they are given antihistaminic drugs. For this reason, the frequency and severity of side effects cannot be predicted. Respiration may be depressed and this effect can be serious in infections involving the airway. Parents and others may have difficulty assessing the intensity of induced side effects and children cannot be expected to understand their potential hazards. For these reasons, medical supervision is recommended when children under 6 years are given antihistaminic drugs.

2. *Category II conditions under which antihistamine ingredients are not generally recognized as safe and effective or are misbranded.* The use of antihistamines under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following labeling should be removed from the market until scientific testing supports their use.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II, paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is de-

scriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antihistamines include statements such as the following:

a. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.*

These include claims such as "specially formulated", "scientifically improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary—".

b. *Claims implying a physiological effect which either have no foundation or meaning or will be meaningless or misleading to the public.* Items include: "gets at the root of—"; "fights"; "wakes up"; "recommended by doctors"; "travels through the blood stream".

c. *Claims for relief where time is indeterminate.* Terms include: "fast"; "prompt".

d. *Claims for relief of nasal symptoms (other than running nose, itchy nose, and sneezing).* Terms include: "decreases nasal obstruction"; "decreases nasal congestion"; "relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an antihistamine must be demonstrated by controlled, double-blind studies because of the subjective nature of both the symptoms and the effects of any drug-induced changes.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antihistamine active ingredients:

Phenyltoloxamine citrate
Thenyldiamine hydrochloride (oral)

a. *Phenyltoloxamine citrate.* The Panel concludes that phenyltoloxamine citrate is safe for OTC use but there are insufficient data available regarding its effectiveness to permit final classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenyltoloxamine citrate is safe in the dose ranges used as an antihistamine. Animal studies have indicated phenyltoloxamine is one of the least toxic antihistamines. As much as 680 mg/kg given orally to rats produced no symptoms. In dogs, 10 mg/kg for 50 days was well tolerated (Ref. 1).

Studies in humans, also suggest a low incidence of side effects at a dosage of 100 to 200 mg in 24 hours with moderate drowsiness occurring following dosage in excess of 200 mg in 24 hours (Ref. 2). One reference states that in therapeutic doses, soporific effects occur in less than 7 percent of patients (Ref. 3). A low incidence of side effects, 6.5 percent, was reported in one study in which allergy patients were given 25 or 50 mg 3 or 4 times daily (Ref. 4). In another study (Ref. 5), phenyltoloxamine was given for its "ataraxic" effect in a dosage of 300 mg daily, 100 mg after lunch for daytime sedation and 200 mg at bedtime for nighttime sedation. Side effects were reported to be minimal in this study.

Sainz (Ref. 6) performed a study in 48 patients to determine side effects and toxicity and found that mild drowsiness appeared at oral doses above 200 mg 4 times daily, or with single doses of 400 mg. Ataxia or abnormal reflexes were not noted at oral doses of 400 mg 4 times a day. There were no extrapyramidal symptoms. The EEG was not affected. A slight blood pressure increase was seen and doses higher than 200 mg 4 times daily produced adrenergic stimulation (increased salivation, gastritis, and diarrhea). Hearburn was found in 14 percent of patients taking the drug, and occasionally nausea was seen. No changes were noted in metabolic, nutritional, endocrine, hematologic, urologic or liver function parameters. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of the dihydrogen citrate salt of phenyltoloxamine at 100 mg (56 mg of the active moiety) 4 times daily.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 423 million dosage units were sold. (See part VII, paragraph A.6. above—Human toxicity.) Of the 90 suspected poisonings reported for phenyltoloxamine citrate, 15.6 percent exhibited some symptoms and 5.6 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of data supplied by the Food and Drug Administration showed only one adverse reaction report on phenyltoloxamine citrate since 1968 (Ref. 7). The adverse reaction was listed as possibly related to abnormal kidney function tests.

The Panel concludes that phenyltoloxamine citrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenyltoloxamine citrate as an antihistamine. Phenyltoloxamine citrate is an antihistamine drug which in animal studies antagonizes most of the pharmacologic actions of histamine (Ref. 1). In clinical use, the drug appears to provide symptomatic relief of allergic symptoms (Refs. 2 and 3), although no controlled studies are available which

permit a determination of the minimum effective dosage level.

Cronk and Naumann (Ref. 2) used a dosage of 25 to 50 mg 4 times daily, but reported "relief" only in patients receiving 50 mg 4 times daily. Seyler and Simon (Ref. 4) likewise recommended a dosage of 50 mg 3 or 4 times daily. Thus, clinical experience indicates a daily dosage of 150 to 200 mg.

The Panel concludes that although there are insufficient data to determine that phenyltoloxamine citrate is effective for the relief of the symptoms of allergic rhinitis, 50 mg is the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours; children age 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII, paragraph C. below—Data Required for Evaluation.)

REFERENCES

- (1) Hoekstra, J. B., D. E. Tisch, N. Rakleten and H. L. Dickison, "Pharmacological Properties of a New Antihistaminic Agent, Phenyltoloxamine (Bristamin)," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 42:587-593, 1953.
- (2) Cronk, G. A. and D. E. Naumann, "Phenyltoloxamine—Dosage, Toxicity and Clinical Application," *New York State Journal of Medicine*, 55:1465-1467, 1955.
- (3) "Phenyltoloxamine Citrate," Council on Pharmacy and Chemistry, *Journal of the American Medical Association*, 163:357, 1957.
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- (5) Fleischmajer, R., S. Blau and N. B. Kanof, "The Mental Action and Antihistaminic Efficacy of Phenyltoloxamine in Cutaneous Disorders," *Antibiotic Medicine and Clinical Therapy*, 5:120-124, 1958.
- (6) Sainz, A., "Studies in Psychic Action of Phenyltoloxamine," *Proceedings of the Mohawk Valley Psychiatric Association*, 1967.
- (7) OTC Volume 040325.

b. *Thenyldiamine hydrochloride (oral).* The Panel concludes that thenyldiamine hydrochloride (oral) is safe for OTC use but there are insufficient data available regarding effectiveness to permit final

classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (oral) is safe in the dosage ranges used as an antihistamine. The Panel has discussed the topical use of this drug as a nasal decongestant elsewhere in this document. (See part VIII. paragraph B.3.k. below—Thenyldiamine hydrochloride (topical).)

This drug was selected from among several related compounds because of marked antihistaminic and anti-anaphylactic properties and its low toxicity in animals (Refs. 1 and 2). Thenyldiamine is relatively nontoxic in animals. The oral LD₅₀ for mice is about 190 mg/kg and for the guinea pig 240 mg/kg. There are no human safety data on the use of thenyldiamine administered orally alone. Data in uncontrolled studies with a combination product containing phenylephrine, acetaminophen and caffeine in addition to thenyldiamine in a dose of 25 to 150 mg daily revealed no significant changes in pulse rate or blood pressure (Refs. 3 and 4). Tabulations of side effects in patients receiving thenyldiamine hydrochloride alone and those receiving the combination formulation are difficult to interpret. The chief side effect appears to be sedation or drowsiness. Dizziness, dryness of the throat, headache, perspiration, and nausea have also been reported (Ref. 1).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 2.5 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) In the one suspected poisoning reported for thenyldiamine hydrochloride, no symptoms were exhibited.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thenyldiamine hydrochloride since 1968 (Ref. 5).

The Panel concludes that thenyldiamine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (oral) as an antihistamine and reports of clinical experience are lacking. Thenyldiamine hydrochloride was official in U.S.P. XII. The dose was 15 mg orally. The frequency of treatment was not stated. A secondary reference source indicates the dosage to be 15 to 30 mg (Ref. 6). It appears that effective adult dosage may not be attained by using the commercially available OTC combination products which contain 2.5 to 7.5 mg per dosage unit.

In vitro studies of 0.03 gamma thenyldiamine in a 20 ml bath gave 75 percent inhibition of a standardized contraction produced by 0.3 gamma histamine. The drug compared well with diphenhydramine and pyrilamine as measured by histamine shock in the guinea pig where

1 mg/kg gave complete protection against the LD₅₀. The drug also gave marked protection against anaphylaxis in the guinea pig.

The Panel concludes that although there are insufficient data to determine that thenyldiamine hydrochloride (oral) is effective for the relief of the symptoms of allergic rhinitis, 15 to 30 mg are the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) However, the Panel recommends that the Category I warning pertaining to use in children be revised from 6 years to 12 years with the following specific labeling: (i) *Warning.* "Do not give this product to children under 12 years except under the advice and supervision of a physician". (ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours; children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

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- (3) OTC Volume 040167.
- (4) OTC Volume 040169.
- (5) OTC Volume 040325.
- (6) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," in "Drill's Pharmacology in Medicine," 4th Ed., Edited by Divalpa, J. McGraw-Hill Co., New York, pp. 763-785, 1971.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antihistamines. Additional data are required to substantiate these claims for OTC antihistamine use: a. The following statements of duration are unacceptable unless documentation can specify the number of hours: "provides hours of relief" "all day" "all night".

b. "Alleviates, decreases or for temporary relief of running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in the common cold".

c. "Alleviates, decreases or for temporary relief of running nose, as may occur in the common cold."

d. "Alleviates, decreases or for temporary relief of sneezing as may occur in the common cold".

e. "Alleviates, decreases or for temporary relief of itching of the nose or throat as may occur in the common cold".

f. "Alleviates, decreases or for temporary relief of itchy and watery eyes as may occur in the common cold".

g. "Dries running nose as may occur in the common cold".

h. *Claims that sleep will be facilitated.* Terms include "promotes restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

1. *Principles in the design of an experimental protocol for testing antihistamine drugs in allergic rhinitis.* a. *General principles.* The antihistaminic drugs are indicated for the symptomatic relief of IgE mediated allergic reactions. (See part II paragraph B.1.—Allergy.) When such reactions occur in the upper airway, the symptoms include sneezing, nasal discharge, nasal obstruction and itching of the nose, eyes, throat and ears. Such symptoms may or may not be accompanied by objective manifestations and for this reason, the patients' subjective sensations must be relied upon in the assessment of drug action. However, observations on the degree of edema of the nasal mucus membrane, the quantity of nasal discharge and the degree of injection of the sclerae may be helpful. The action of this group of drugs is limited to a few hours so that repeated doses at regular intervals are required for a sustained effect. All the antihistamines have side effects which again are subjective and have virtually no objective counterpart. Because of the subjective nature of both the symptoms and the effect of any drug-induced change, double-blind experimental control is especially important in the assessment of antihistaminic drugs.

Considerable experience in assessing therapy for allergic rhinitis caused by pollen (hay fever) has accumulated in the past 15 or more years in the course of efforts to determine the effectiveness of injection therapy (immunotherapy). Hitherto unrecognized problems in the selection of cases, the recording and scoring of symptoms, the tally of medication other than preparation(s) under test and the maintenance of experimental control became apparent (Ref. 1).

b. *Selection of patients.* The selection of patients should be limited of those

giving a clear history of having had allergic symptoms (hay fever) in at least two consecutive annual pollen seasons, who are free from symptoms at other times of the year, who react intensely to prick or scratch test with an extract of appropriate pollen and who are otherwise in good general health. Patients who are not undergoing treatment with injections of allergenic extracts are preferred in the study.

The diagnosis of allergic rhinitis depends on both a history of the symptoms occurring at the times of allergenic exposure and their absence at other times, and the presence of intense relevant immunologic reactivity commonly determined by skin test. The patient's statements as to the time of year when symptoms occur may be in error. Therefore, documentation of the occurrence of symptoms at the time of exposure and the absence of symptoms at other times by observation of the patient is preferable to the history. Patients who react intensively by skin test to one pollen usually react to several other pollens also. Some of the reactions obtained by skin test may be irrelevant, a positive skin test being a necessary but not sufficient basis for identifying the cause of the symptoms. Thus the limitations of the history and the skin test need to be taken into account.

c. *Methods of study.* Assessment of therapy is based on a subjective response. Therefore, some means of quantitating symptoms must be adopted. Experience has indicated that this can be done satisfactorily by maintaining a daily tally of symptoms specifying type, e.g., sneezing, rhinorrhea, etc., duration in hours per day and intensity. Most patients have little difficulty in describing intensity numerically if they are given an intensity scale wherein points on the scale are defined by statements indicating the degree of discomfort (Refs. 2 and 3). Assignment of a numerical value to the degree of discomfort is space saving and greatly facilitates analysis of the data. However, account should be taken of the burden that a diary imposes on the patient. If too detailed and complicated, patients lose interest and record their symptoms in a perfunctory manner with the result that the data may be worthless. Some compromise between what is ideal and what is practicable must be reached. A satisfactory compromise was one in which the patient was given a symptom score card covering 1 week of study, to be filled out at the end of each day. The patient returned with the card at the end of each week at which time the patient was interviewed and the card rechecked for comprehensibility (Ref. 2). A new card was then supplied.

In a double-blind study which includes a placebo, some patients will suffer severe symptoms and the patient's continuation in the study will thereby be jeopardized. If the design of the study does not permit withdrawal from the study because of severe symptoms as an endpoint, then the investigator will be under great pressure to prescribe or permit use of medication other than the preparations under test or

the patient will take medication without reporting having done so. Such medications, if taken, should be recorded accurately on the weekly diary form. Before the study is started, each such drug should be assigned a numerical value per dose based on anticipated efficacy in relieving symptoms of allergic rhinitis. The data may then be incorporated into the analysis at the end of the study.

A placebo identical in appearance and closely similar or identical in taste to the preparation(s) under test must be included in any assessment of drugs for the treatment of allergic rhinitis. Assignment of subjects to the drug(s) under test and the placebo must be random and the code identifying the preparations administered must not be broken until the study is complete.

Patients should be seen throughout the season not less often than every week. Patient diaries should be maintained in which the type, frequency and severity of symptoms and side effects are recorded daily as well as the medication taken. A crossover double-blind design with 30 or more patients is recommended in which each patient takes the test drug or the placebo on alternate weeks. If two dose levels of the test drug are tested, twice the number of patients will be needed.

d. *Interpretation of data.* Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. Evidence of drug effectiveness is required from a minimum of three positive studies based on results from three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(5) *Evaluation of safety.* The effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines the central nervous system is often affected as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity which might pose a hazard to the patient in the performance of a daily routine.

REFERENCES

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(3) Sadan, N. et al., "Immunotherapy of Pollinosis in Children. Investigation of the Immunologic Basis of Clinical Improvement," *New England Journal of Medicine*, 280:623-627, 1969.

2. *Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold."* a. *Assessment of the use of antihistaminic drugs for the "common cold."* The antihistaminic drugs have been widely used for the treatment of the symptoms of the

"common cold." These drugs are usually marketed in combination products with nasal decongestant drugs. It is the Panel's view that this use of the antihistaminic drugs has been based predominantly on clinical impressions and uncontrolled clinical trials, the first of which was published by Brewster in 1947 (Ref. 1). On the other hand, a number of trials have been conducted with double-blind experimental controls but have failed for the most part to substantiate claims for effectiveness. These negative results indicate that if the antihistaminic drugs indeed have a favorable effect on the symptoms of the "common cold," this effect must be of a relatively low order. The subject has been recently reviewed (Ref. 2). The Panel concurs with the authors who stated:

Many of the reports favoring antihistamine use were published some years ago when a well-controlled, randomized, double-blind clinical trial was not generally recognized as important in the evaluation of therapy. However, results supporting antihistamine use should be interpreted with caution when the research goals are imprecise and the study design permits biases. On the other hand, the findings of the less favorable reports that antihistamines appear not to prevent, abort, or relieve the symptoms of a cold, are supported by only a slightly greater specificity of definition and increased rigor of research methodology. Of all the Reports, only two combined precision in definitions and controlled design; their conclusions did not support the use of antihistamines to prevent or relieve the symptoms of a cold. The general lack of specificity in defining disease and research goals and lack of rigor in research design in the majority of all studies is noteworthy. In short, there appears to be little valid evidence that antihistamines have any effect on the common cold.

Studies on the efficacy of the antihistaminic drugs in the treatment of the "common cold" may be misleading if the means of selection do not minimize inadvertent inclusion of subjects with allergic rhinitis, the symptoms of which are similar to those of the "common cold." Relief of symptoms will then be erroneously ascribed to favorable effect of the antihistaminic drugs on the symptoms of the "common cold" when indeed the observed benefit may be attributable to the known efficacy of the antihistaminic drugs in allergic rhinitis. The Panel has earlier discussed in this document both the "common cold" and allergic rhinitis. (See part II, paragraph B.3. above—The "common cold" and part II, paragraph B.6.a. above—Allergic rhinitis.)

The Panel concludes that the effectiveness of the antihistaminic drugs in relieving or allaying the symptoms of the "common cold" has not been established. If further studies on the effectiveness of the antihistaminic drugs in the treatment of the "common cold" are to be carried out, the Panel suggests that particular attention be directed to the selection of subjects and the means of recording symptoms using groups of patients large enough to give statistically meaningful results.

b. *General principles.* The symptoms of allergic rhinitis and the "common cold" have many similarities. A watery

nasal discharge is characteristic of allergic rhinitis and is usual in the "common cold" in the first 1 to 3 days. Sneezing is likewise common to both. Itching of the nose and eyes is more common in allergic rhinitis but also occurs in the "common cold." Nasal congestion occurs in both conditions. Coughing is not a frequent symptom of allergic rhinitis but it occurs in a small percent of cases. Cough likewise occurs in the "common cold," usually in the latter phase of the illness. Fever of low degree may occur in the "common cold," but it is not frequently present. Fever is absent in allergic rhinitis. Watery and redness of the eyes may occur in both conditions (Refs. 3, 4, and 5).

It is commonly stated in texts on allergic disease that examination of the patient with allergic rhinitis reveals swelling within the nose (swollen turbinates) which has a bluish or gray color (Ref. 5), whereas in the "common cold" their color is red (Ref. 4). No studies have been done to test the frequency with which this distinction is diagnostic and its reliability as a means of selecting patients for inclusion in a study of antihistaminic drugs in the treatment of the "common cold" remains uncertain. No other finding on examination appears to be useful in distinguishing between the early phases of the "common cold" and allergic rhinitis.

Because the symptoms of allergic rhinitis and the "common cold" are so similar, the two conditions are readily confused. The reported efficacy of the antihistaminic drugs in the treatment of the "common cold" has been attributed to the inadvertent inclusion of some cases of allergic rhinitis in some studies (Ref. 2) in which condition the antihistaminic drugs are recognized as effective. Unless steps are taken to eliminate subjects with allergic rhinitis from the study population, the results of the study of the "common cold" may be misleading.

c. *Selection of patients.* Since the distinction between allergic rhinitis and the "common cold," especially in its early phases, is difficult or impossible to make on the basis of symptoms and examination, the following means of minimizing inclusion of subjects with symptoms of allergic rhinitis should be adopted:

(1) Subjects giving a history of allergic rhinitis, e.g., hay fever or allergy to animals, should be excluded.

(2) Studies should be done in the months when allergic exposure is less likely and the "common cold" is more prevalent.

Selection of subjects according to these principles will minimize but cannot entirely eliminate the inclusion of some subjects who are having symptoms of allergic rhinitis and not a "common cold."

Subjects selected for the studies should be in good health except for the presence of a "common cold." The symptoms to be evaluated, i.e., runny nose, sneezing, etc., should have been present for 1 day but not longer than 3 days. Fever should be absent or should not exceed 100° F by mouth (adults) or 101° F by mouth

(children under 12 years). Those with evidence of bacterial infection of the pharynx (exudative pharyngitis) or who have severe pharyngitis and severe sore throat should be excluded.

d. *Methods of study.* The drug(s) to be tested and a placebo should be identical in appearance and closely similar in taste identifiable by code only. Strict double-blind control throughout the study is essential. The groups of subjects should be matched by age, sex and severity and duration of illness.

Each group should contain 50 to 100 subjects. This large number is considered mandatory for the following reasons: a crossover design is not possible in so short an illness; the assessment is based on a subjective response; there are uncertainties in diagnosis; there is possible heterogeneity of the study population with respect to the type of virus causing the illness; and the effect of the antihistaminic drug in relieving symptoms of the "common cold" is not marked.

Medication other than the preparations in the test should not be taken during the course of the study. The design of the study should be such as to permit determination of each preparation's effect on each type of symptom and the stage in the disease in which this effect takes place. Therefore, each subject should maintain an appropriate tally of the type, duration and intensity of symptoms. The study should be of sufficient length to encompass the entire illness to provide data on all possible effects of the drug under test on the course of the disease. If a subject drops out of the study, the reason for doing so should be determined and recorded.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Interpretation of data.* A recommended dose of the antihistamine should induce a statistically significant reduction in symptoms when compared to the placebo response. Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. A decision on drug effectiveness should be based on demonstrable drug effectiveness in a minimum of three positive comparable double-blind studies based on results from three different investigators or laboratories.

f. *Evaluation of safety.* If the safety of the drug has not been established, then the effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines, the central nervous system is often affected, as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity that might pose a hazard to the patient in the performance of a daily routine.

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VIII. NASAL DECONGESTANTS

A. GENERAL DISCUSSION

A nasal decongestant is an agent which reduces nasal congestion in patients with acute or chronic rhinitis. These agents may be administered topically as drops, sprays or inhaled vapors or orally in a solid or liquid dosage form. The drug effect is brought about by constriction of dilated blood vessels (vasoconstriction) within the nasal mucosa, thus temporarily reducing the swelling associated with inflammation of the mucous membrane lining the nasal passage (Ref. 1).

Topically administered nasal decongestants produce an intense degree of vasoconstriction, a factor responsible for the rapid and pronounced reduction in nasal obstruction. This intense local vasoconstriction also accounts for negligible absorption of the nasal decongestant into the general circulation. Consequently, negligible systemic effects occur following topical use of nasal decongestants unless excessive nasal solution is applied causing drainage into the stomach where it may be absorbed. Studies demonstrating minimal systemic absorption of radioactively labeled oxymetazoline following intranasal application (Ref. 2) and negligible cardiovascular effects following normal and excessive intranasal doses of phenylephrine or xylometazoline (Refs. 3 through 7) support this point. Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days.

Another practical caution with the use of topically applied decongestants is in regard to the possible spread of infection if the drug dispenser is used by more than one person. This can occur if the tip of the dropper or spray container comes in contact with the nose during drug administration.

Some of the nasal decongestants (sympathomimetic amines) are also effective when administered orally. Although the intensity of vasoconstriction in the nasal mucosa and associated symptomatic re-