

NOTICES

days after the date of publication hereof in the FEDERAL REGISTER may cause the drug to be subject to regulatory proceedings.

3. The notice "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study" published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), describes in paragraphs (d), (e), and (f) the marketing status of a drug labeled with those indications for which it is regarded as possibly effective.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 12152, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (Identify with NDA number):
Office of Scientific Evaluation (BD-100),
Bureau of Drugs.

Original new drug applications: Office of
Scientific Evaluation (BD-100), Bureau of
Drugs.

Requests for the Academy's report: Drug
Efficacy Study Information Control (BD-
67), Bureau of Drugs.

All other communications regarding this an-
nouncement: Drug Efficacy Study Imple-
mentation Project Office (BD-60), Bureau
of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: June 27, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-10456 Filed 7-7-72;8:48 am]

[DESI 4084]

CERTAIN OTC BRONCHODILATORS AND ANTI-ASTHMATIC PREPARATIONS

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has received reports from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, for the over-the-counter drugs listed below. Pending the results of the OTC study of drugs in this class, action on these reports will be deferred in accordance with the proposal published in the FEDERAL REGISTER of April 20, 1972 (37 F.R. 7807) entitled "Over-the-Counter Drugs" concerning the status of drugs previously reviewed under the Drug Efficacy Study.

The following OTC bronchodilators and antiasthmatic drugs are included in this announcement:

1. Enofen Tablets containing phenobarbital, theophylline, and ephedrine sulfate; Kremers-Urban Co., 5600 West County Line Road, Mequon, Wis. 53201 (NDA 4-084).

2. Tedral and Tedral Half Strength Enteric Coated Tablets containing phenobarbital, theophylline, and ephedrine hydrochloride; Warner-Chilcott Laboratories, Div. Warner-Lambert Pharmaceutical Co., 201 Tabor Road, Morris Plains, N.J. 07950 (NDA 4-508).

The evaluations of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, Panel on Drugs Used in Allergy, and Panel on Drugs Used in Respiratory Disturbances are as follows:

1. Enofen tablets containing phenobarbital, theophylline, and ephedrine sulfate.

PANEL ON DRUGS USED IN ALLERGY

Indication: Bronchial asthma.

Evaluation: Effective, but * * *

Comments: Oral ephedrine in 25-mg. dosage is an effective drug in bronchial asthma, and phenobarbital is a useful additive to counteract the excitatory effects of ephedrine. Oral theophylline in the hydrous form, however, is absorbed irregularly, and is of doubtful value in this combination. Although there is no direct available published evidence on blood levels after oral theophylline (hydrous), it seems unlikely, by analogy with other theophylline compounds, that this dose will produce therapeutically useful blood levels of theophylline.

This indication was reevaluated as possibly effective with the following additional comment:

However, in view of recent evidence that the inhibitory effect of theophylline on phosphodiesterase may supplement the adenylyl cyclase-stimulating action of sympathomimetics in inhibiting mediator release in immediate hypersensitivity, it is possible that the theophylline could act synergistically with ephedrine at dosage levels not in themselves effective. However, this has not been shown clinically.

General comments: The insert should warn that some patients develop acute urinary retention as a side effect of ephedrine. This occurs most commonly in men with prostatic hypertrophy, but it has been reported to occur in some women as well.

PANEL ON DRUGS USED IN RESPIRATORY DISTURBANCES

Indication: Bronchial asthma.

Evaluation: Effective, but * * * (Subsequently reevaluated as possibly effective.)

Comments: There is no evidence that this product is more effective than ephedrine alone. Theophylline is probably ineffective at the dosage suggested.

The Panel objects to the inclusion of phenobarbital in this product. If sedation is necessary in the management of a patient with severe asthma or emphysema, it should be given independently of other medications so that the effects and side effects of each can be individually controlled. However, combinations of ephedrine and phenobarbital are often useful in patients with mild episodic asthma.

2. Tedral and Tedral Half Strength Enteric Coated Tablets containing phenobarbital, theophylline, and ephedrine hydrochloride.

PANEL ON DRUGS USED IN ALLERGY

Indication: Bronchial asthma.

Evaluation: Possibly effective.

Comments: Oral ephedrine in 25-mg. dosage is an effective drug in bronchial asthma, and phenobarbital is a useful additive to counteract the excitatory effects of ephedrine. Oral theophylline (hydrous) is absorbed irregularly, and is of doubtful value in this combination. The properties of en-

teric coating are not well documented, and if delayed absorption results from the enteric coating, effective levels of ephedrine may not be attained.

Indication: Hay fever.

Evaluation: Possibly effective.

Comments: The Panel fails to discern the rationale for giving theophylline in hay fever.

PANEL ON DRUGS USED IN RESPIRATORY DISTURBANCES

Indication: Bronchial asthma.

Evaluation: Possibly effective.

Comments: The properties of this specific product have not been defined. Because of the enteric coating of this product, suitable clinical studies must be done to establish its efficacy. If absorption of the ingredients is not hindered, the effectiveness of the product would be due to the ephedrine, because oral theophylline is probably ineffective at the dosage suggested.

The Panel objects to the inclusion of phenobarbital in this product when it is used in patients with severe asthma. If sedation is necessary in the management of a patient with asthma, it should be given independently of other medications so that the effects and side effects of each can be individually controlled. However, combinations of ephedrine and phenobarbital are often useful in patients with mild episodic asthma.

A copy of the Academy's report has been furnished to each firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 4084, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Requests for the Academy's report: Drug
Efficacy Study Information Control (BD-
67), Bureau of Drugs.

All other communications regarding this an-
nouncement: Drug Efficacy Study Imple-
mentation Project Office (BD-60), Bureau
of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: April 28, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-14050 Filed 7-7-72;8:47 am]

[DESI 1205]

CERTAIN OTC COLD REMEDIES Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has received reports from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, for the over-the-counter drugs listed below. The Academy's reports constitute an important element of the totality of information considered by the Administration in reaching its conclusions concerning the effectiveness of drugs in the Drug Efficacy Study and the marketing

status of such drugs under the Federal Food, Drug, and Cosmetic Act.

It is recognized that, although the over-the-counter drug products reviewed by the Academy are relatively few in number, they are representative of many such preparations on the market—preparations which are identical, similar, or related, and competitive. Although some of the other marketed articles differ qualitatively and/or quantitatively and some bear labeling claims different from those reviewed by the Academy, they generally contain ingredients which are of the same pharmacologic class as those reviewed by the Academy. Therefore, questions raised by the Academy about the drugs they reviewed are applicable to related or identical drugs not under review, and the Academy's ratings may be applicable as well.

It is recognized that new evidence of effectiveness may have become available since 1966 when the then-existing evidence was submitted to the Academy for review. It is also known that for many drugs substantial evidence in support of at least some of their recommended uses is not available.

The need for review of all over-the-counter drugs by class for safety, effectiveness, and adequate labeling has become apparent. The undertaking of a major study of these drugs by the Administration with the assistance of advisory committees was announced in the FEDERAL REGISTER, May 11, 1972. To facilitate the development of a consistent policy for each class of OTC drugs and to insure equitable treatment of all firms marketing competitive over-the-counter drugs, further implementation of the Drug Efficacy Study as it pertains to the OTC drugs listed here and related OTC drugs is deferred pending the results of the OTC study. (See "Over-the-Counter Drugs" 37 F.R. 7807, a proposal describing the status of OTC drugs reviewed under the Drug Efficacy Study.)

However, in order to make available to interested persons the opinions of the Drug Efficacy Study Group of the National Academy of Sciences-National Research Council, their evaluation and comment on each drug are set forth below.

The following OTC drugs are included in this announcement:

1. Isophrin Nose Drop Solution containing phenylephrine hydrochloride; Broemmel Pharmaceuticals, 1235 Sutter Street, San Francisco, Calif. 94109 (NDA 16A).
2. Propadrine Hydrochloride Elixir containing phenylpropanolamine hydrochloride; Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486 (NDA 1-205).
3. Privine Hydrochloride Nasal Jelly, Nasal Solution, and Nasal Spray containing naphazoline hydrochloride; Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 556 Morris Avenue, Summit, N.J. 07901 (NDA 5-070).
4. Tuamine Inhaler containing tuaminoheptane and menthol, Eli Lilly and Co., Post Office Box 618, Indianapolis, Ind. 46205 (NDA 5-172).

5. Tagathen Tablets containing chlorpheniramine citrate, Lederle Laboratories, Division American Cyanamid Co., Pearl River, N.Y. 10965 (NDA 6-331).

6. Histadyl and A.S.A. Compound Pulvules containing methapyrilene hydroxybenzoyl benzoate, aspirin, phenacetin and caffeine; Eli Lilly and Co. (NDA 6-340).

7. Benzedrex Inhaler containing propylhexadrine and menthol; Smith Kline and French Laboratories, 1500 Spring Garden Street, Philadelphia, Pa. 19101 (NDA 6-410).

8. Decapryn with Aspirin, Phenacetin, and Caffeine Tablets containing doxylamine succinate, aspirin, phenacetin, and caffeine; Merrell-National Laboratories, Division of Richardson-Merrell Inc., 110 East Amity Road, Cincinnati, Ohio 45215 (NDA 6-412).

9. Forthane Inhaler containing methylhexanamine; Eli Lilly & Co. (NDA 6-444).

10. Antistine-Privine Nasal Solution containing antazoline hydrochloride and naphazoline hydrochloride; Ciba Pharmaceutical Co. (NDA 6-456).

11. Wyamine Inhaler containing mephentermine and menthol; Wyeth Laboratories, Division of American Home Products Corp., Post Office Box 8299, Philadelphia, Pa. 19101 (NDA 6-569).

12. Wyamine Sulfate Nasal Solution containing mephentermine sulfate; Wyeth Laboratories (NDA 6-652).

13. Clopane Hydrochloride Solution containing cyclopentamine hydrochloride; Eli Lilly and Co. (NDA 6-666).

14. Coricidin Cold Tablets containing chlorpheniramine maleate, aspirin and caffeine; Schering Corp., 60 Orange Street, Bloomfield, N.J. 07003 (NDA 6-921).

15. Thephorin-AC Tablets containing phenindamine tartrate, aspirin, phenacetin and caffeine; Roche Laboratories, Division of Hoffmann-La Roche Inc., 340 Kingsland Avenue, Nutley, N.J. 07110 (NDA 7-026).

16. Vasoxyil Nasal Solution & Spray containing methoxamine hydrochloride; Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, N.C. 27709 (NDA 7-239).

17. Bena-Fedrin Solution containing diphenhydramine hydrochloride and ephedrine hydrochloride; Parke, Davis & Co., Joseph Campau at the River, Detroit, Mich. 48232 (NDA 7-652).

18. Inhiston-APC Tablets containing pheniramine maleate, aspirin, phenacetin and caffeine; Pharmaco/Sardo Products, Division Plough, Inc., 3022 Jackson Avenue, Memphis, Tenn. 38101 (NDA 7-812).

19. Bristamin APC Tablets containing phenyltoloxamine citrate, aspirin, phenacetin and caffeine; Bristol Laboratories, Inc., Division of Bristol-Myers Co., Thompson Road, Post Office Box 657, Syracuse, N.Y. 13201 (NDA 8-828).

20. Phenylpropanolamine Hydrochloride Nyscap Timed Release Capsule; Nysco Laboratories, Inc., 34-24 Vernon Boulevard, Long Island City, N.Y. 11106 (NDA 10-789).

21. Fedrazil Tablets containing chlorcyclizine hydrochloride and pseudoephedrine hydrochloride; Burroughs Wellcome Co. (NDA 11-876).

22. Nasalair Inhaler containing isocyclamine, Isodine Pharmacal Corp., Division of International Latex Corp., Dover, Del. 19901 (NDA 12-094).

23. Quadrin Tablets containing acetaminophen, phenyltoloxamine citrate, and phenylpropanolamine hydrochloride; The Norwich Pharmacal Co., Post Office Box 191, Norwich, N.Y. 13815 (NDA 12-207).

24. Contac Sustained Release Capsules containing chlorpheniramine maleate, phenylpropanolamine hydrochloride, atropine sulfate, scopolamine hydrobromide, and hyoscyamine sulfate; Menley & James Laboratories, 1500 Spring Garden Street, Philadelphia, Pa. 19101 (NDA 12-686).

25. Chlorephrine Nyscaps containing chlorpheniramine maleate and phenylephrine hydrochloride; Nysco Laboratories, Inc., (NDA 12-755).

26. Tri-Span 12-Hour Decongestant Tablets containing acetaminophen, pyrilamine maleate, caffeine, ephedrine sulfate, and phenylpropanolamine hydrochloride; Vick Chemical Co., Division of Richardson-Merrell Inc., 122 East 42d Street, New York, N.Y. 10017 (NDA 12-849).

27. Ampar Timed Release Capsules containing chlorpheniramine maleate and phenylephrine hydrochloride; United Pharmaceuticals, Inc., 1064 44th Avenue, Oakland, Calif. 94601 (NDA 13-397).

The National Academy of Sciences-National Research Council, Drug Efficacy Study Group, Panel on Drugs for Relief of Pain, made the following General Statements on Analgesic Preparations, which are applicable to any of these products that make analgesic claims.

GENERAL STATEMENTS ON ANALGESIC PREPARATIONS

EVIDENCE FOR GENERAL ANALGESIC EFFECT

It is the recommendation of the Panel that, when a drug has been shown to be an effective analgesic in several different kinds of clinical pain, by suitably controlled trials using modern criteria, such a drug be entitled to consideration as an "all-purpose analgesic" unless special considerations indicate that this is not appropriate. In such cases, it would seem desirable to allow the drug to be marketed for the relief of most kinds of pain, thus avoiding the necessity for listing specific conditions.

ANALGESIC MIXTURES

There is increasing evidence, which has accumulated particularly within the past few years, that it is not always easy to predict the effects of adding one drug to another. Thus, drugs may merely summate in their activities, antagonize each other, or produce true potentiation. Since adequate trials on the relative efficacy of single drugs and mixtures are usually unavailable, it is hard for the Panel to be both fair and scientific in the evaluation of many of the mixtures which it has been asked to review.

Furthermore, some ingredients appear to have been added to these mixtures on the basis of a rationale that is not evident to the Panel. On other occasions, the rationale

seems evident, but the reason for the particular doses chosen (especially those which seem homeopathic) is not clear.

In addition to the well-known objections that fixed-ratio mixtures do not allow flexibility in the doses of individual ingredients, one can object to many analgesic mixtures because they contribute little additional therapeutic benefit while increasing the risks of side effects, allergic sensitization, etc. One can perhaps justify the use of some of these mixtures when pain is present with some other symptom, such as a stuffy nose, and both symptoms can be handled reasonably well by the mixture. However, to promote such a mixture as an all-purpose remedy for all kinds of pain, including those which cannot possibly be aided by one or more of the ingredients, is, in the view of the Panel, to encourage bad therapeutics.

SEMANTIC CONFUSION

The words "synergism" and "potentiation" are subject to multiple interpretations, even among professional pharmacologists. It would seem desirable to avoid their use, focusing instead on a description of what actually was achieved in the clinical setting. The word "potency" also has different meanings to different persons. If one is talking simply about milligram potency, this is actually a trivial matter in the clinical setting and, therefore, the term "potency" should probably be avoided.

IRRELEVANT INFORMATION

Many package inserts contain material of no relevance to most practitioners. For example, the animal data are often not helpful, and are not always clearly identifiable as such. This material often seems to be used as a substitute for clinical data. Also irrelevant and not particularly helpful to the reader is a long list of clinical testimonials, only some of which bear on the points at issue, and most of which are uninterpretable because of defects in clinical design.

DRUG DEPENDENCE AND ABUSE

The following statement is proposed to bring uniformity to the claims made concerning the dependence-producing properties of narcotic analgesics and preparations containing narcotic analgesics. It is recognized that many of the claims concerning a lesser dependence-producing liability of specific narcotic analgesics reflect the fact that the particular agents are not commonly abused. However, it must also be recognized that the actual abuse rates do not accurately reflect dependence-producing potential. It is known that agents and preparations that have not been commonly abused in some social settings at some times, have been extensively abused in other settings at other times.

One of the major purposes of the existing laws and regulations concerning narcotic analgesics is to prevent abuse. Therefore, all agents that have been shown to produce morphine-like physiologic and subjective changes when administered chronically, that will produce morphine-like dependence, or that will substitute for morphine in morphine-dependent subjects, shall carry the following recommended warning:

(Name of agent) can produce dependence of the morphine type and therefore has the potential for being abused.

The only exceptions to this recommendation are substances specifically exempted from bearing the label "Warning—may be habit forming" required by Federal law or regulation.

RIGID DOSE RECOMMENDATIONS

The Panel believes that doctors should not be bound legally by dose recommendations in package inserts. These recommendations

represent advice as to the dose at which most patients can be started, and the range at which the needs of most patients can be met. However, it is good practice to manipulate the dose in the event of a therapeutic failure, or in the event of untoward effects. Furthermore, tolerance to a drug may develop, and may require an increase in dose. It is the Panel's observation that some of the recommended doses are too low.

DEFICIENCIES OF METHODOLOGY

There is a need for additional methodology for the study of pain. Thus, for example, there is a paucity of information available on the comparative effects of analgesics given repeatedly to patients with chronic pain. The result with single doses may or may not be transferable to such situations. Another area of deficiency is the evaluation of topical ointments that produce obvious sensations of cooling or warmth. Such limitations in methodology should be kept in mind by the Food and Drug Administration when evaluating data on drugs, both old and new.

The evaluations of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, are as follows:

1. Isophrin Nose Drop Solution containing phenylephrine hydrochloride. This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Symptomatic relief (of nasal congestion) in colds, sinusitis, and hay fever. Evaluation: Effective.

Comments: None.

General comments: The insert should warn that prolonged or excessive use of this product may result in rebound nasal congestion.

It should be noted that use of the 1.0 percent solution may result in a high incidence of side effects.

2. Propadrine Hydrochloride Elixir containing phenylpropanolamine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Hay fever and allergic rhinitis. Evaluation: Probably effective.

Comments: The Panel believes that this product is effective, but adequately controlled clinical studies have not been presented.

3. Privine Hydrochloride Nasal Jelly, Nasal Solution, and Nasal Spray containing naphazoline hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion, as in colds, sinusitis, and hay fever.

Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product, but adequate documentation has not been provided.

4. Tuamine Inhaler containing tuaminoheptane and menthol.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion.

Evaluation: Possibly effective.

Comments: Data relevant to this mode of administration of this compound have not been presented to the Panel.

5. Tagathen Tablets containing chlorothen citrate.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Temporary relief of nasal congestion, watering of the eyes, running nose and sneezing due to hay fever or rose fever.

Evaluation: Possibly effective.

Comments: Adequate documentation of the clinical effect of this compound at the recommended dose has not been presented to the Panel.

6. Histadyl and A.S.A. Compound Pulvules containing methapyriline hydroxybenzoyl benzoate, aspirin, phenacetin, and caffeine.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of symptoms of the common cold.

Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

General comments: A warning about the dangers of use by aspirin-sensitive patients should be included on the label.

7. Benzedrex Inhaler containing propylhexadrine and menthol.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Temporary relief of nasal congestion in colds and hay fever; also for ear block and pressure pain during air travel.

Evaluation: Probably effective.

Comments: Although the Panel believes that this product is effective, adequately controlled studies supporting its efficacy have not been presented.

8. Decapryn with aspirin, phenacetin and caffeine tablets containing doxylamine succinate, aspirin, phenacetin, and caffeine.

This drug has been evaluated by the following Panels:

- Panel on Drugs Used in Allergy.
- Panel on Drugs for Relief of Pain.

PANEL ON DRUGS USED IN ALLERGY

Indication: Temporary relief of minor discomforts associated with the common cold.

Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

General comments: A warning about the dangers of use by aspirin-sensitive patients should be included on the label.

PANEL ON DRUGS FOR RELIEF OF PAIN

Indication: For the temporary relief of minor discomforts associated with the common cold.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic combination, APC, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredient would detract from or add to this effect.

This combination is probably capable of relieving many different kinds of pain. However, there are no specific, well-controlled, and conclusive studies on the above-mentioned conditions.

9. Forthane Inhaler containing methylnhexaneamine.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion.
Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product, but adequate documentation has not been provided.

10. Antistine-Privine Nasal Solution containing antazoline hydrochloride and naphazoline hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Symptomatic relief of nasal congestion due to allergic rhinitis; vasomotor rhinitis; acute, subacute or chronic sinusitis.

Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product. However, adequate documentation does not seem to be available.

Indication: The decongestive action of this combination is more intense and prolonged in many instances than that produced by either antihistamine or decongestant solution alone.

Evaluation: Possibly effective.

Comments: The Panel is unaware of any acceptable evidence to support this.

General comments: The insert should warn that prolonged or excessive use of this product may result in rebound nasal congestion.

11. Wyamine Inhaler containing mephentermine and menthol.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Temporary relief of nasal congestion.

Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product. However, adequately controlled studies do not seem to be available.

12. Wyamine Sulfate Nasal Solution containing mephentermine sulfate.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Nasal decongestion in acute or chronic rhinitis, sinusitis, and allergic rhinitis (hay fever and perennial or vasomotor rhinitis).

Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product. However, adequately controlled studies do not seem to be available.

General comments: The labeling should warn that prolonged or excessive use of this product may result in rebound nasal congestion.

13. Clopane Hydrochloride Solution containing cyclopentamine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Nasal congestion due to hay fever, vasomotor rhinitis, or the common cold, sinusitis; preoperative vasoconstriction of nasal and nasopharyngeal mucosa; and epistaxis due to nasal congestion.

Evaluation: Probably effective.

Comments: This judgment is based on

physiologic studies, in the absence of adequate clinical studies.

General comments: The insert should warn that excessive or prolonged use of this product may result in rebound nasal congestion.

14. Coricidin Cold Tablets containing chlorpheniramine maleate, aspirin, and caffeine.

This drug has been evaluated by the following Panels:

a. Panel on Drugs Used in Allergy.

b. Panel on Drugs for Relief of Pain.

PANEL ON DRUGS USED IN ALLERGY

Indication: Symptomatic relief of colds and accompanying aches, pain, fever, and simple headache.

Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

General comments: The presence of aspirin in this combination should be clearly identified and a warning about the dangers of use by aspirin-sensitive patients should be included on the label.

PANEL ON DRUGS FOR RELIEF OF PAIN

Indication: For symptomatic relief of colds and accompanying aches, pains, fever, and simple headache.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic aspirin, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredients would detract from or add to this effect.

15. Thephorin-AC Tablets containing phenindamine tartrate, aspirin, phenacetin, and caffeine.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of "cold symptoms."

Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

General comments: A warning about the dangers of use by aspirin-sensitive patients should be included on the label.

16. Vasoxyd nasal solution and spray containing methoxamine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Temporary relief of nasal congestion.

Evaluation: Probably effective.

Comments: In the experience of the Panel, this is an effective product. However, adequately controlled studies do not seem to be available.

General comments: The labeling should warn that excessive or prolonged use of this product may result in rebound nasal congestion.

17. Bena-fedrin solution containing diphenhydramine hydrochloride, and ephedrine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of congestion of the mucous membrane of the nose and throat.

Evaluation: Effective, but * * *.

Comments: No data have been presented to the Panel that demonstrate the superiority of this combination to ephedrine alone. No data demonstrating the local effect of the antihistamine have been presented to the Panel, other than some data regarding local anesthetic properties. The usefulness of Chlorotone (chlorobutanol) has not been demonstrated.

The potential risk of sensitization to topically applied antihistamines is such that the Panel prefers the oral route. As indicated above, antihistaminic efficacy is not well established for most of these drugs when they are applied directly to the nasal mucosa.

This indication was reevaluated as possibly effective with the following comments:

No data has been presented to the Panel demonstrating benefit in adding antihistamine or Chlorotone to the mixture.

The potential risk of sensitization to topically applied antihistamines is such that the Panel feels this is another reason not to use the preparation.

Finally, the label should warn that prolonged or excessive use of this product may result in rebound nasal congestion.

General comments: The label should warn that prolonged or excessive use of this product may result in rebound nasal congestion.

18. Inhiston-APC Tablets containing pheniramine maleate, aspirin, phenacetin, and caffeine.

This drug has been evaluated by the following Panels:

a. Panel on Drugs Used in Allergy.

b. Panel on Drugs for Relief of Pain.

PANEL ON DRUGS USED IN ALLERGY

Indication: Symptomatic relief of colds.
Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

Indication: Hay fever.

Evaluation: Possibly effective.

Comments: The APC component probably does not add to the effect of the antihistamine. Pheniramine probably is an effective antihistamine when taken in adequate dosage. The amount of antihistamine present in this product is below that found to be effective in the experience of the Panel.

General comments: A warning about the dangers of use by aspirin-sensitive patients should be included on the label.

PANEL ON DRUGS FOR RELIEF OF PAIN

Indication: For symptomatic relief of aches, pains, colds, hay fever, and simple headaches.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic combination, APC, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredient would detract from or add to this effect.

This combination is probably capable of relieving many different kinds of pain. However, there are no specific, well-controlled, and conclusive studies on the above-mentioned conditions.

General comments: Whether the addition of the antihistamine contributes anything additional to the management of the clinical entities of "aches, pains, and simple headache" is not known.

19. Bristamin-APC Tablets containing phenyltoloxamine citrate, aspirin, phenacetin, and caffeine.

This drug has been evaluated by the following Panels:

- a. Panel on Drugs Used in Allergy.
- b. Panel on Drugs Used in Dentistry.
- c. Panel on Drugs for Relief of Pain.

PANEL ON DRUGS USED IN ALLERGY

Indication: Symptomatic relief of colds.

Evaluation: Effective, but * * * (subsequently reevaluated as ineffective as a fixed combination).

Comments: It has not been proved that the antihistamine contributes to the relief of these symptoms provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

General comments: A warning about the dangers of use by aspirin-sensitive patients should be included on the label.

PANEL ON DRUGS USED IN DENTISTRY

Indication: To aid in the relief of pain and discomfort following tooth extraction or other dental work.

Evaluation: Possibly effective.

Comments: There is no question that APC is effective in controlling pain of dental origin. However, the Panel questions the role of phenyltoloxamine in the listed claims, and further questions its low dosage. The Panel feels that the company should substantiate phenyltoloxamine in this dosage as effective in the treatment of the listed conditions.

PANEL ON DRUGS FOR RELIEF OF PAIN

Indication: Pain-relieving compound with antihistamine.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic combination, APC, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredient, Bristamin, would detract from or add to this effect.

Indication: For relief of discomfort from colds, headaches, minor menstrual and dental pain.

Relieves muscular aches and pains, feverish feeling, headache.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic, APC, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredient, Bristamin, would detract from or add to this effect.

This combination is probably capable of relieving many different kinds of pain. However, there are no specific, well-controlled,

and conclusive studies on the above-mentioned conditions.

General comments: Whether the addition of the antihistamine contributes anything additional to the management of the clinical entities of "aches, pains, and simple headache" is not known.

20. Phenylpropanolamine Hydrochloride Nyscap Timed Release Capsule: This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion due to the common cold.

Evaluation: Possibly effective.

Comments: No data supporting this claim have been presented to the Panel.

Indication: Relief of nasal congestion due to hay fever and nasal stuffiness.

Evaluation: Probably effective.

Comments: Nasal stuffiness is a symptom not a diagnosis.

Indication: Timed release produces prolonged effect.

Evaluation: Possibly effective.

Comments: No data supporting this claim have been presented to the Panel.

21. Fedrazil Tablets containing chlorcyclizine hydrochloride and pseudoephedrine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion associated with colds.

Evaluation: Possibly effective (subsequently reevaluated as ineffective as a fixed combination).

Comments: There is no evidence that either drug in this combination will accomplish what is claimed. The dose of pseudoephedrine is less than optimal for many adults and it has not been proved to be beneficial for this indication. It has not been proved that the antihistamine contributes to the relief of cold symptoms which is provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

Indication: Hay fever.

Evaluation: Effective.

Comments: The dose of pseudoephedrine is less than optimal for many adults.

22. Nasalaire Inhaler containing isocyclamine.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: For instant relief of nasal congestion accompanying colds, hay fever, sinus trouble, allergies, catarrh, postnasal drip.

Evaluation: Possibly effective.

Comments: The documentation provided by the manufacturer is inadequate proof of clinical efficacy. The terms "allergies" and "postnasal drip" are insufficiently precise.

General comments: If this product is found to be effective, the labeling should be revised to include adequate instructions for its use. Contraindications and side effects should be mentioned and a warning that prolonged or excessive use of the product may result in rebound nasal congestion should be included.

23. Quadrin Tablets containing acetaminophen, phenyltoloxamine citrate, and phenylpropanolamine hydrochloride.

This drug has been evaluated by the following Panels:

- a. Panel on Drugs Used in Allergy.

b. Panel on Drugs for Relief of Pain.

PANEL ON DRUGS USED IN ALLERGY

Indication: Relief of nasal congestion due to common colds and hay fever.

Evaluation: Possibly effective.

Comments: Adequate documentation of these claims has not been supplied. Phenyltoloxamine is a weak antihistamine, in the experience of the Panel, and there is no controlled study supporting its usefulness in colds. Acetaminophen has no effect on nasal congestion known to the Panel, although it is a known analgesic.

No data supporting claims about speed and duration of action have been presented to the Panel.

PANEL ON DRUGS FOR RELIEF OF PAIN

Indication: New Quadrin's acid-free formula works without aspirin to shut out pain. Quadrin's new analgesic acetaminophen is safer, faster than aspirin.

Evaluation: Effective, but * * *.

Comments: This combination contains the known analgesic, acetaminophen, which at the recommended dose would provide relief of pain. There is no reason to expect that the additional ingredients would detract from or add to this effect.

The first part of the claim is certainly correct; the compound contains no aspirin. The other claims are questionable. If the manufacturer means that there is less risk of gastrointestinal bleeding, it should say so. The claim that the compound works faster than aspirin is not substantiated by any available evidence.

24. Contac Capsules containing chlorpheniramine maleate, phenylpropanolamine hydrochloride, atropine sulfate, scopolamine hydrobromide, and hyoscyamine sulfate.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Relief of nasal congestion of the common cold.

Evaluation: Possibly effective.

Comments: No supporting data, collected in a controlled fashion, have been presented to the Panel. It is doubtful that the antihistamine is of benefit for the relief of nasal congestion due to the common cold. Several carefully controlled studies, in which different antihistamines were tried, disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

This indication was subsequently reevaluated as ineffective as a fixed combination with the following additional comments:

It has not been proved that the antihistamine contributes to the relief of cold symptoms which is provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds.

Indication: Relief of nasal congestion due to hay fever.

Evaluation: Probably effective.

Comments: The dose recommended would provide much less than the optimal amount of chlorpheniramine for the average adult with hay fever. A dose three times as great was used in the references cited.

The variability in individual responsiveness to belladonna alkaloids makes it unlikely that many patients would get much benefit from the small, fixed dose of these compounds contained in Contac.

Indication: 12-hour effect.

Evaluation: Possibly effective.

[DESI 8709]

**CERTAIN PARENTERAL DRUGS
CONTAINING VERATRUM ALKALOIDS****Drugs for Human Use; Drug Efficacy
Study Implementation**

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following antihypertensive drugs:

1. Veralba Injection containing protoveratrine A and B; the Dow Chemical Co., 1200 Madison Avenue, Indianapolis, Ind. 46225 (NDA 8-709).

2. Unitensin Aqueous containing cryptenamine acetates; Mallinckrodt Chemical Works, 3600 North Second Street, St. Louis, Mo. 63160 (NDA 8-814).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new-drug application is required from any person marketing such drug without approval.

A. Effectiveness classification. The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that these drugs are effective for short-term use in the treatment of hypertensive crises:

B. Conditions for approval and marketing. The Food and Drug Administration is prepared to approve abbreviated new-drug applications and abbreviated supplements to previously approved new-drug applications under conditions described herein.

1. **Form of drug.** These veratrum alkaloid preparations are aqueous solutions suitable for parenteral administration.

2. **Labeling conditions.** a. The labels bear the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drugs are labeled to comply with all requirements of the Act and regulations. Their labeling bears adequate information for safe and effective use and, where applicable, the Academy's comments. The "Indications" sections are as follows:

INDICATIONS

For short-term use in the treatment of hypertensive crises.

3. **Marketing status.** Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER, July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new-drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraphs (a)(1)(i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new-drug ap-

Comments: Controlled clinical data supporting the 12-hour action of this product have not been presented to the Panel.

25. **Chlorephrine Nyscaps** containing chlorpheniramine maleate and phenylephrine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Nasal congestion due to hay fever.

Evaluation: Effective.

Comments: None.

Indication: Nasal congestion due to the common cold.

Evaluation: Possibly effective.

Comments: Adequate evidence supporting this claim has not been presented to the Panel. In addition, it is doubtful whether the antihistamine is of benefit for the relief of symptoms due to the common cold. Several carefully controlled studies, in which different antihistamines were tried, disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

This indication was subsequently reevaluated as ineffective as a fixed combination with the following additional comments:

Indication: Relief of nasal congestion associated with colds.

There is no evidence that either drug in this combination will accomplish what is claimed. The dose of pseudoephedrine is less than optimal for many adults and it has not been proved to be beneficial for this indication. It has not been proved that the antihistamine contributes to the relief of cold symptoms which is provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds.

Indication: Timed-release capsule.

Evaluation: Effective.

Comments: None.

26. **Vicks Tri-Span 12-Hour Decongestant Tablets** containing acetaminophen, pyrilamine maleate, caffeine, ephedrine sulfate, and phenylpropanolamine.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Symptomatic relief of nasal congestion due to colds.

Evaluation: Probably effective (subsequently reevaluated as ineffective as a fixed combination).

Comments: Although the acetaminophen and caffeine may provide some relief of "headache, achy feeling of colds," it is doubtful whether they contribute to the relief of nasal congestion, which appears to be the major indication for which this product is sold. The antihistamine may provide some benefit in cases of hay fever, but is probably not of use in colds. No supporting data, collected in a controlled fashion, have been presented to the Panel. It is doubtful whether the antihistamine is of benefit for the relief of nasal congestion due to the common cold. Several carefully controlled studies, in which different antihistamines were tried, disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

Indication: 12-hour effect.

Evaluation: Possibly effective.

Comments: Controlled clinical data supporting this claim have not been presented to the Panel.

Indication: Symptomatic relief of nasal congestion due to hay fever.

Evaluation: Probably effective.

Comments: None.

27. **Ampar Timed Release Capsules** containing chlorpheniramine maleate and phenylephrine hydrochloride.

This drug has been evaluated by the Panel on Drugs Used in Allergy.

Indication: Nasal congestion due to hay fever.

Evaluation: Probably effective.

Comments: Adequate evidence supporting this claim has not been presented to the Panel.

Indication: Nasal congestion due to the common cold.

Evaluation: Possibly effective.

Comments: Adequate evidence supporting this claim has not been presented to the Panel. In addition, it is doubtful whether the antihistamine is of benefit for the relief of symptoms due to the common cold. Several carefully controlled studies, in which different antihistamines were tried, disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds. When allergic rhinitis is mistaken for a cold, antihistamines may be of benefit; but allergic rhinitis is being treated in that instance, not an upper respiratory infection.

This indication was subsequently reevaluated as ineffective as a fixed combination with the following additional comments.

There is no evidence that either drug in this combination will accomplish what is claimed. The dose of pseudoephedrine is less than optimal for many adults and it has not been proved to be beneficial for this indication. It has not been proved that the antihistamine contributes to the relief of cold symptoms which is provided by this combination. The majority of carefully controlled studies that have been performed with antihistamines disclosed no alleviation of symptoms or shortening of the duration of symptoms of colds.

Indication: Time-released capsule.

Evaluation: Possibly effective.

Comments: No unequivocal data regarding this property have been submitted to the Panel.

A copy of the Academy's report has been furnished to each firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 1205, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Requests for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 120).

Dated: June 26, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

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