

1715 West 38th Street, Chattanooga, Tenn. 37409 (NDA 6-158).

4. Theoglycinate with phenobarbital tablets containing theophylline sodium glycinate and phenobarbital; Brayten Pharmaceutical Co. (NDA 6-158).

5. Theoglycinate with racebookrine and phenobarbital tablets containing theophylline sodium glycinate, phenobarbital, and racebookrine hydrochloride; Brayten Pharmaceutical Co. (NDA 6-158).

6. Phedorine tablets (formerly Theophedrine with phenobarbital tablets) containing theophylline, phenobarbital, and ephedrine hydrochloride; Tilden-Yates Laboratories, Inc., Fairfield Road, Wayne, N.J. 07470 (NDA 1-626).

7. Asminyl tablets and asminyl slosol pink tablets containing theophylline, sodium phenobarbital, and ephedrine sulfate; Cole Pharmacal Co., Inc. (NDA 3-523).

8. Asminyl liquid containing theophylline sodium salicylate, sodium butabarbital, and ephedrine sulfate; Cole Pharmacal Co., Inc. (NDA 3-523).

9. Arteminyl sublingual tablets (now marketed as Iso-Asminyl) containing theophylline, sodium phenobarbital, isoproterenol hydrochloride, and ephedrine sulfate; Cole Pharmacal Co., Inc. (NDA 3-523).

10. Marax syrup containing theophylline, hydroxyzine hydrochloride, and ephedrine sulfate; J. B. Roerig Division, Pfizer Pharmaceuticals, 235 East 42d Street, New York, NY 10017 (NDA 12-879).

11. Marax tablets containing theophylline, hydroxyzine hydrochloride, and ephedrine sulfate; J. B. Roerig Division, Pfizer Pharmaceuticals (NDA 11-768).

AMBUPHYLLINE PREPARATIONS

1. Nethaphyl regular strength capsules and nethaphyl half strength capsules containing ambuphylline, ephedrine hydrochloride, and phenobarbital; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 110 East Amity Road, Cincinnati, Ohio 45215 (NDA 6-359).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). The effectiveness classification and marketing status are described below.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that:

1. *Rectal suppositories containing theophylline sodium glycinate as the sole active ingredient.* a. Are probably effective for bronchial asthma.

b. Are possibly effective as labeled for use in status asthmaticus, congestive heart failure, or as a diuretic in congestive heart failure, paroxysmal cardiac dyspnea, coronary artery diseases and angina, allaying pruritis, and relieving sensitization dermatoses.

c. Lack substantial evidence of effectiveness as labeled for use in Cheyne-Stokes respiration and "bronchospastic

type chronic hypertrophic pulmonary emphysema."

2. *Other drugs listed in this announcement.* a. These drugs lack substantial evidence of effectiveness as labeled for use in "pulmonary infections associated with bronchospasm," dyspnea induced by exertion and cough, Cheyne-Stokes respiration, status asthmaticus, "bronchospastic type of chronic hypertrophic pulmonary emphysema," "other pulmonary disorders," or as a sedative.

b. These drugs are possibly effective as labeled for use in bronchial asthma; bronchitis, bronchiectasis, and emphysema in which bronchospasm is present; paroxysmal cardiac or nocturnal dyspnea; biliary colic, renal colic; hay fever; congestive heart failure or as a diuretic in congestive heart failure, premenstrual fluid retention and drug induced edema; coronary artery disease and angina pectoris; allaying pruritis and in relieving sensitization dermatoses; pulmonary edema due to cardiac decompensation; the relief of bronchospasm; nasal allergy; or for use as respiratory center stimulants and expectorants.

B. *Marketing status.* 1. Within 60 days of the date of publication of this announcement in the FEDERAL REGISTER, the holder of any approved new drug application for which a drug is classified in paragraph A above as lacking substantial evidence of effectiveness is requested to submit a supplement to his application, as needed, to provide for revised labeling which deletes those indications for which substantial evidence of effectiveness is lacking. Such a supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest possible time, and the revised labeling should be put into use within the 60-day period. Failure to do so may result in a proposal to withdraw approval of the new drug application.

2. If any such preparation is on the market without an approved new-drug application, its labeling should be revised if it includes those claims for which substantial evidence of effectiveness is lacking as described in paragraph A above. Failure to delete such indications and put the revised labeling into use within 60 days after the date of publication hereof in the FEDERAL REGISTER may cause the drug to be subject to regulatory proceedings.

3. Labeling revised pursuant to this notice should take into account the comments of the Academy; furnish adequate information for safe and effective use of the drug; and recommend use of the drug having a probably effective indication as follows: (The possibly effective indications for that drug may also be included in the labeling for 6 months.)

RECTAL SUPPOSITORIES CONTAINING THEOPHYLLINE SODIUM GLYCINATE

INDICATION

Bronchial Asthma.

4. The notice "Conditions for Marketing New Drugs Evaluated in the Drug

Efficacy Study" published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), describes in paragraphs (c), (d), (e), and (f) the marketing status of a drug labeled with those indications for which it is regarded as probably effective and possibly effective.

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 1626, 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 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 2.120).

Dated: June 28, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-11518 Filed 7-25-72; 8:46 am]

[DESI 11145; Docket No. FDC-D-322; NDA 11-145 et al.]

CERTAIN THIAZIDES

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 single entity thiazide drugs:

1. Fovane Tablets, containing benzthiazide; marketed by Chas. Pfizer and Co., 235 East 42d Street, New York, NY 10017 (NDA 12-128).

2. Esidrix Tablets, containing hydrochlorothiazide; marketed by Ciba Pharmaceutical Co., 556 Morris Avenue, Summit, NJ 07901 (NDA 11-793).

3. Exna Tablets, containing benzthiazide; marketed by A. H. Robins Co., 1407 Cummings Drive, Richmond, VA 23220 (NDA 12-489).

4. Saluron Tablets, containing hydroflumethiazide; marketed by Bristol Laboratories, Division of Bristol-Myers Co., Thompson Road, Post Office Box 657, Syracuse, NY 13201 (NDA 11-949).

5. Renese Tablets, containing polythiazide; Chas. Pfizer & Co. (NDA 12-845).

6. Metahydrin Tablets, containing tri-chloromethiazide; marketed by Lakeside Laboratories, Division of Colgate-Palmolive Co., 1707 East North Avenue, Milwaukee, WI 53201 (NDA 12-594).

7. Diuril Syrup, containing chlorothiazide; marketed by Merck Sharp & Dohme, Division of Merck and Company, Inc., West Point, Pa. 19486 (NDA 11-870).

8. Diuril Lyovac Powder for Injection, containing chlorothiazide as the sodium salt; Merck Sharp & Dohme (NDA 11-145).

9. Diuril Tablets, containing chlorothiazide; Merck Sharp and Dohme (NDA 11-145).

10. Naqua Tablets, containing tri-chloromethiazide; marketed by Schering Corp., 60 Orange Street, Bloomfield, NJ 07003 (NDA 12-265).

11. Hydrodiuril Tablets, containing hydrochlorothiazide; Merck Sharp & Dohme (NDA 11-835).

12. Enduron Tablets, containing methyclothiazide; marketed by Abbott Laboratories, 14th Street and Sheridan Road, North Chicago, Ill. 60064 (NDA 12-524).

13. Oretic Tablets, containing hydrochlorothiazide; Abbott Laboratories (NDA 11-971).

14. Naturetin Tablets, containing ben-droflumethiazide; marketed by E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 12-164).

15. Saluron Syrup, containing hydroflumethiazide; Bristol Laboratories (NDA 12-058).

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:

1. These thiazide drugs in the dosage forms listed above are effective as adjunctive therapy in the treatment of edema due to congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen administration; and edema caused by renal disorders such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure; in the management of hypertension when used alone or as adjunctive therapy; in the control of hypertension in pregnancy; and severe or marked edema when due to pregnancy. The routine use of diuretics in an otherwise healthy pregnant woman is contraindicated and possibly hazardous.

2. These drugs are probably effective for treatment of toxemia of pregnancy; angina accompanying congestive heart failure and/or hypertension; and "drug induced" edema.

3. The drugs are possibly effective for treatment of edema of localized origin; prevention of the development of toxemia during pregnancy; and premenstrual acne flare.

4. The drugs lack substantial evidence of effectiveness for the following claimed indications: "All" types of edema; edema of obesity; edema due to premenstrual tension; fluid retention masked by obesity; and prevention of edema of pregnancy.

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.* Such preparations are in a form suitable for oral administration. Chlorothiazide, as the sodium salt, is a powder suitable for reconstitution and intravenous 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 and their labeling bears adequate information for safe and effective use of the drug.

Those parts of the labeling indicated below are substantially as follows:

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTION

The mechanism of action results in an interference with the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency. The mechanism whereby thiazides function in the control of hypertension is unknown.

INDICATIONS

----- is indicated as adjunctive (Drug) therapy in edema associated with congestive heart failure, hepatic cirrhosis and corticosteroid and estrogen therapy.

----- has also been found useful in (Drug) edema due to various forms of renal dysfunction as:

Nephrotic syndrome;
Acute glomerulonephritis; and
Chronic renal failure.

----- is indicated in severe edema (Drug) when due to pregnancy. (See "Contraindications" and "Warnings" below.)

Diuretics are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in the more severe forms of hypertension and in the control of hypertension of pregnancy.

The drug is also indicated in toxemia of pregnancy (eclampsia); angina due to congestive heart failure and/or hypertension; and "drug induced" edema.

For intravenous chlorothiazide add: Use only when patients are unable to take oral medication.

CONTRAINDICATIONS

Anuria.
Hypersensitivity to this or other sulfonamide derived drugs.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS

Should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USAGE IN PREGNANCY

Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS

Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: Dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is

not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS

A. GASTROINTESTINAL SYSTEM REACTIONS

- | | |
|-----------------------|--|
| 1. anorexia | 7. constipation |
| 2. gastric irritation | 8. jaundice (intra-hepatic cholestatic jaundice) |
| 3. nausea | 9. pancreatitis |
| 4. vomiting | |
| 5. cramping | |
| 6. diarrhea | |

B. CENTRAL NERVOUS SYSTEM REACTIONS

- | | |
|-----------------|---------------|
| 1. dizziness | 4. headache |
| 2. vertigo | 5. xanthopsia |
| 3. parasthesias | |

C. HEMATOLOGIC REACTIONS

- | | |
|--------------------|---------------------|
| 1. leukopenia | 3. thrombocytopenia |
| 2. agranulocytosis | 4. aplastic anemia |

D. DERMATOLOGIC—HYPERSENSITIVITY REACTIONS

- | | |
|---------------------|--|
| 1. purpura | 5. necrotizing anginitis (vasculitis) (cutaneous vasculitis) |
| 2. photosensitivity | |
| 3. rash | |
| 4. urticaria | |

E. CARDIOVASCULAR REACTION

Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

F. OTHER

- | | |
|------------------|-----------------|
| 1. hyperglycemia | 4. muscle spasm |
| 2. glycosuria | 5. weakness |
| 3. hyperuricemia | 6. restlessness |

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. This therapy should be titrated to gain maximal therapeutic response as well as the minimal dose possible to maintain that therapeutic response.

Parenteral therapy should be reserved for patients unable to take oral medication or in emergency situations.

The usual daily dosages for antihypertensive and diuretic effect are roughly comparable as well as the oral and parenteral dosages.

	Diuretic	Antihypertensive	Pediatric
Chlorothiazide...	0.5 to 2 Gm.	0.5 to 2 Gm.	Under 6 months: 10 to 15 mg./lb/day.
Hydrochlorothiazide.	25 to 200 mg.	25 to 100 mg.	Under 6 months: 1 to 1.5 mg./lb/day.
Hydroflumethiazide.	25 to 200 mg.	50 to 100 mg.	
Bendroflumethiazide.	2.5 to 20 mg.	2.5 to 20 mg.	
Benzthiazide.....	50 to 200 mg.	50 to 200 mg.	
Polythiazide.....	1 to 4 mg.	2 to 4 mg.	
Trichlormethiazide.	1 to 4 mg.	2 to 4 mg.	
Methychlothiazide.	2.5 to 10 mg.	2.5 to 10 mg.	

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 Oct. 10, 1962), the submission of a supplement for revised labeling, an abbreviated supplement for updating information, and adequate data to show the biologic availability of the drug in the formulation which is marketed as described in paragraphs (a) (1) (i), (ii), and (iii) of the notice of July 14, 1970. Clinical trials which have established effectiveness of the drug may also serve to establish the bioavailability of the drug if such trials were conducted on the currently marketed formulation.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application, to include adequate data to assure the biologic availability of the drug in the formulation which is or is intended to be marketed, as described in paragraph (a) (3) (ii) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

d. For indications for which the drug has been classified as probably effective (included in the "Indications" section above), and possibly effective (not included in the "Indications" section above), continued use as described in paragraphs (c), (d), (e), and (f) of that notice.

C. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Any related drug for human use, not the subject of an approved new drug application offered for the indications for which substantial evidence of effectiveness is lacking may be affected by this action.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355), and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days

after the date of publication of this notice in the FEDERAL REGISTER.

3. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing, together with a well-organized and full factual analysis of the clinical and other investigational data that the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a) (5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

4. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

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 11145, 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 abbreviated new drug applications (Identify as such): Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

Request for Hearing (Identify with Docket Number): Hearing Clerk, Office of General Counsel (GC-1), Room 6-88, Parklawn Building.

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.

Received requests for a hearing may be seen in the office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

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 29, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 72-11521 Filed 7-25-72; 8:44 am]