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: July 14, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11645 Filed 7-26-72;8:50 am]

[DESI 8627]

CERTAIN DRUGS CONTAINING ACETYLDIGITOXIN, DESLANOSIDE, DIGITOXIN, OR DIGOXIN

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 drugs for oral or parenteral use:

1. Lanoxin Injection containing digoxin; Burroughs Wellcome & Co., Inc., 3030 Cornwallis Road, Research Triangle Park, NC 27709 (NDA 9–330).

2. Cedilanid-D Injection containing deslanoside; Sandoz Pharmaceuticals, Division of Sandoz-Wander, Inc., Route 10, Hanover, N.J. 07936 (NDA 9–282).

3. Digitaline Nativelle Intramuscular containing digitoxin; E. Fougera & Co. Inc., Cantigue Road, Post Office Box 73, Hicksville, Long Island, NY 11802 (NDA 8–627).

4. Acylanid Tablets containing acetyldigitoxin; Sandoz Pharmaceuticals (NDA 9–436).

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 reports, as well as other available evidence, and concludes that oral preparations containing acetyldigitoxin and parenteral preparations of deslanoside, digitoxin, or digoxin are effective for use in the treatment of congestive heart failure, supraventricular tachycardia (paroxysmal atrial or nodal), atrial flutter, and atrial fibrillation.

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.* Acetydigitoxin preparations are in a tablet dosage form suitable for oral administration. Deslanoside, digitoxin, and digoxin preparations are in sterile aqueous solution form suitable for parenteral administration.

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

b. The drug is labeled to comply with all requirements of the Act and regulations promulgated thereunder and those parts of its labeling indicated below are substantially as follows:

CARDIAC (DIGITALIS) GLYCOSIDES LABELING GUIDELINE (ADULT)

DESCRIPTION

The cardiac (or digitalis) glycosides are a closely related group of drugs having in common specific and powerful effects on the myocardium. These drugs are found in a number of plants. The term "digitalis" is used to designate the whole group. Typically, the glycosides are composed of three portions, a steroid nucleus, a lactone ring, and a sugar (hence "glycosides").

(This section should include a chemical and/or physical description of the drug, a sterility statement when appropriate, and the same quantitative ingredient information as that required on the label.)

ACTION

The digitalis glycosides have qualitatively the same therapeutic effect on the heart. They (1) increase the force of myocardial contraction, (2) increase the refractory period of the atrioventricular (A–V) node, and (3) to a lesser degree, affect the sinoatrial (S–A) node and conduction system via the parasympathetic and sympathetic nervous systems.

(Insert additional specific information relative to absorption and excretion, onset of action, peak effect, duration of effect, etc.)

INDICATIONS

1. "Congestive heart failure," all degrees, is the primary indication. The increased cardiac output results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digitalis, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digitalis should be continued after failure is abolished unless some known precipitating factor is corrected.

2. "Atrial fibrillation"—especially when the ventricular rate is elevated. Digitalis rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concommitant congestive failure ameliorated.

Digitalis is continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. "Atrial flutter" digitalis slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digitalis at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digitalis if failure ensues or if atrial flutter is a frequent occurrence.

4. "Paroxysmal atrial tachycardia" digitalis may be used, especially if it is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if failure has ensued or paroxysms recur frequently, digitalis is maintained by oral administration.

Digitalis is not indicated in sinus tachycardia or premature systoles in the absence of heart failure.

"Cardiogenic shock"—the value of digitalis is not established, but the drug is often employed, especially when the condition is accompanied by pulmonary edema. Digitalis seems to adversely affect shock due to infections.

CONTRAINDICATIONS

The presence of toxic effects (See "Overdosage") induced by any digitalis preparation is an absolute contraindication to all of the glycosides.

"Allergy," though rare, does occur. It may not extend to all preparations and another may be tried.

VENTRICULAR FIBRILLATION

"Ventricular tachycardia," unless congestive failure supervenes after a protracted episode not itself due to digitalis.

WARNINGS

Many of the arrhythmias for which digitalis is advised are identical with those reflecting digitalis intoxication. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digitalis intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

PRECAUTIONS

"Potassium depletion" sensitizes the myocardium to digitalis and toxicity is apt to develop even with usual dosage. Hypokalemia also tends to reduce the positive inotropic effect of digitalis.

Potassium wastage may result from diuretic, corticosteroid, hemodialysis and other therapy. It is apt to accompany malnutrition, old age and long-standing congestive heart failure.

"Acute myocardial infarction," severe pulmonary disease, or far advanced heart failure are apt to be more sensitive to digitalis and more prone to disturbances of rhythm.

"Calcium" affects contractility and excitability of the heart in a manner similar to that of digitalis. Calcium may produce serious arrhythmias in digitalized patients.

"Myxedema"—Digitalis requirements are less because excretion rate is decreased and blood levels are significantly higher.

"Incomplete AV block," especially patients subject to Stokes Adams attacks, may develop advanced or complete heart block. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

"Chronic constrictive pericarditis," is apt to respond unfavorably.

"Idiopathic hypertrophic subaortic stenosis" must be managed extremely carefully. Unless cardiac failure is severe it is doubtful whether digitalis should be employed.

"Renal insufficiency" delays the excretion of digitalis and dosage must be adjusted accordingly in patients with renal disease.

NOTE: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require adjustment of digitalis dosage.

ADVERSE REACTIONS

Gynecomastia, uncommon.

OVERDOSAGE, TOXIC EFFECTS

"Gastrointestinal"—anorexia, nausea, vomiting, diarrhea—are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants).

Uncontrolled heart failure may also produce such symptoms.

"Central Nervous System"—headache, weakness, apathy, visual disturbances.

CARDIAC DISTURBANCES

Arrhythmias—"ventricular premature beats" is the most common, except in infants and young children.

Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (inference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digitalis overdosage.

Conduction Disturbances—excessive slowing of the pulse is a clinical sign of digitalis overdosage. Atrioventricular block of increasing degree, may proceed to complete heart block.

NOTE: The electrocardiogram is fundamental in determining the presence and nature of these toxic disturbances. Digitalis may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

TREATMENT OF TOXIC ARRHYTHMIAS

Digitalis is discontinued until after all signs of toxicity are abolished. This may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided doses totaling 4 to 6 gm. for adults (See Pediatric Information for children) provided renal function is adequate.

When correction of the arrhythmia is urgent, potassium is administered intravenously in a solution of 5 percent dextrose in water, a total of 40–100 mEq. (40 mEq. per 500 ml.) at the rate of 40 mEq. per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Electrocardiographic monitoring is indicated to avoid potassium toxicity, e.g. peaking of T waves.

CAUTION

Potassium should not be used and may be dangerous for severe or complete heart block due to digitalis and not related to any tachycardia.

Chelating agents to bind calcium may also be used to counteract the arrhythmia effect of digitalis toxicity, hypokalemia and of elevated serum calcium which may also precipitate digitalis toxicity.

Four grams (0.8 percent solution) of the disodium salt of EDTA is dissolved in 500 ml. of 5 percent dextrose in water (50 mg. per ml.) and administered over a period of 2 hours unless the arrhythmia is controlled before the infusion is completed.

A continuous electrocardiogram should be observed so that the infusion may be promptly stopped when the desired effect is achieved.

Other counteracting agents are: Quindine, procainamide, and beta adrenergic blocking agents.

DOSAGE AND ADMINISTRATION

(Include only for Oral or for Parenteral, as applicable.)

"Oral"—digitalis is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. This amount can be predicted approximately from the weight of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures which may require considerable modification as dictated by individual sensitivity or associated conditions. (See Warning and Precautions)

(Complete by adding dosages—the initial, the maintenance, and the range—for the specific preparation.)

"Parenteral" administration should be used only when the drug cannot be taken orally, or rapid digitalization is very urgent.

(Complete by adding dosages for the specific preparation.)

PEDIATRIC INFORMATION

(If pediatric dosage is available the labeling sections above should be expanded to include the following information.)

WARNINGS

Newborn infants during first month of life have a sharply defined tolerance to digitalis. Impaired renal function must also be carefully taken into consideration.

"Premature and immature infants" are particularly sensitive and further reduction of dosage may be necessary.

Congestive failure accompanying acute "glomerulonephritis" requires extreme care in digitalization. A relatievly low total dose administered in divided doses and concomitant use of reserpine or other antihypertensive agents has been recommended. Constant ECG monitoring is essential and digitalis discontinued as soon as possible.

IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

See Adult Precautions.

"Rheumatic carditis"—such cases, especially when severe, are unusually sensitive to digitalis and prone to disturbances of rhythm. If heart failure develops, digitalization may be tried with relatively low doses; then cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

NOTE: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS

Dosage must be carefully titrated.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

OVERDOSAGE EFFECTS

Toxic signs differ from the adult in a number of respects.

Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and ophthalmological disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms and paroxysmal atrial tachycardia with AV block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF TOXIC ARRHYTHMIAS

(See section for adults.) Potassium preparations may be given orally in divided doses totaling 1–2 gm. daily in children. When correction of the arrhythmia is urgent, 5 to 10 mEq. of potassium per hour are given, this amount being dissolved in 100 ml. of 5 percent dextrose in water. Additional amounts of potassium may be given if necessary and well tolerated by the child.

A chelating agent may be tried if other measures fail. EDTA intravenously has been recommended in a dose of 15 mg./kg./hr. in 5 percent dextrose in water, the total not to exceed 60 mg./kg./day. A continuous electrocardiogram should be observed so that the infusion can be stopped promptly when the desired effect is achieved.

DOSAGE AND ADMINISTRATION

Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive permitting reduced dosage which must be determined by careful titration.

Oral dosage. Newborn (normal), from birth to 1 month, require adult proportions by body weight.

Infants, 1 month to 2 years require approximately 50 percent more by body weight than adult proportions.

Children, 2 years and over require adult proportions by body weight.

(Complete by adding dosage for the specific preparation.)

Long term use of digitalis is indicated in almost all infants who have been digitalized for acute congestive failure unless the cause is transient. Many favor maintaining digitalis until at least 2 years of age in all infants with paroxysmal atrial tachycardia or who show either definite or latent failure.

Many children with severe inoperable congenital defects need digitalis throughout childhood and often for life.

Parenteral dosage. (Include where appropriate.)

Intravenous (or intramuscular, if suitable) use should be reserved for emergencies or when digitalis cannot be taken by mouth. Great care should be exercised if the patient had received a digitalis preparation within the previous 2 weeks.

Intravenous doses should be given slowly with continuous electrocardiographic monitoring to avoid toxic doses.

Intramuscular is less desirable since it may result in a painful local reaction. The volume should not be in excess of 2 cc. and the site should be massaged afterward.

Dosage.

Intramuscular—¾ of oral dose
Intravenous—⅔ of oral dose

NOTE: Digitoxin is an exception to this rule.

(Complete by adding more specific information for specific preparation.)

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, 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 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.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth herein. Requests for such meetings should be made to the Office of Scientific Evaluation (BD-100), at the address given below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

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 8627, 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.

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: July 7, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11633 Filed 7-26-72;8:49 am]

[DESI 597]

CERTAIN DRUGS CONTAINING AN ANTICHOLINERGIC WITH A BARBITURATE

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 drugs for oral administration:

1. Bentyl Syrup with Phenobarbital containing dicyclomine hydrochloride and phenobarbital; Merrell-National Laboratories, Division of Richardson-Merrell Inc., 110 East Amity Road, Cincinnati, Ohio 45215 (NDA 7-961).

2. Bentyl with Phenobarbital Capsules containing dicyclomine hydrochloride and phenobarbital; Merrell-National Laboratories (NDA 7-409).

3. Bentyl Repeat Action Tablets with Phenobarbital containing dicyclomine hydrochloride and phenobarbital; Merrell-National Laboratories (NDA 9-311).

4. Dactil with Phenobarbital Tablets containing piperidolate hydrochloride and phenobarbital; Lakeside Laboratories Inc., Division of Colgate-Palmolive Co., 1707 East North Avenue, Milwaukee, Wis. 53201 (NDA 8-907).

5. Antrenyl-Phenobarbital Tablets contaning oxyphenonium bromide and phenobarbital; Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 556 Morris Avenue, Summit, N.J. 07901 (NDA 8-492).

6. Robinul-PH and Robinul-PH Forte Tablets each containing glycopyrrolate and phenobarbital; A. H. Robins Co., 1407 Cummings Drive, Richmond, Va. 23220 (NDA 12-950).

7. Piptal-PHB Tablets and Elixir each containing pipenzolate bromide and phenobarbital; Lakeside Laboratories Inc. (NDA 9-427).

8. Tricoloid with Phenobarbital Tablets containing tricyclamol chloride and phenobarbital; Burroughs Wellcome & Co., Inc., 3030 Cornwallis Road, Research Triangle Park, N.C. 27709 (NDA 8-910).

9. Co-Elorine 100 and Co-Elorine 25 Pulvules containing tricyclamol chloride and amobarbital; Eli Lilly and Company, Post Office Box 618, Indianapolis, Ind. 46206 (NDA 8-919).

10. Nactisol Tablets containing poldine methylsulfate and sodium butabarbital; McNeil Laboratories, Inc., Camp Hill Road, Fort Washington, Pa. 19034 (NDA 12-741).

11. Phenobarbital and Atropine Tablets containing atropine sulfate and phenobarbital; The Vale Chemical Co., Inc., 1201 Liberty Street, Allentown, Pa. 18102 (NDA 597).

12. Centrine Tablets with Phenobarbital containing aminopentamide sulfate and phenobarbital; Bristol Laboratories, Division of Bristol-Myers Co., Thompson Road, Post Office Box 657, Syracuse, N.Y. 13201 (NDA 9-288).

13. Centrine Elixir with Phenobarbital conatining aminopentamide sulfate and phenobarbital; Bristol Laboratories (NDA 8-885).

14. Profenil Phenobarbital Tablets containing alverine citrate and phenobarbital; Smith, Miller & Patch, Inc., 401 Joyce Kilmer Avenue, New Brunswick, N.J. 08902 (NDA 6-471).

15. Cantil with Phenobarbital Tablets containing mepenzolate bromide and phenobarbital; Lakeside Laboratories, Inc. (NDA 10-679).

16. Valpin-PB Tablets containing anisotropine methylbromide and phenobarbital; Endo Laboratories Inc., 1000 Stewart Avenue, Garden City, Long Island, N.Y. 11533 (NDA 13-430).

17. Valpin-Pb Elixir containing anisotropine methylbromide and phenobarbital; Endo Laboratories, Inc. (NDA 13-431).

18. Banthine with Phenobarbital Tablets containing methantheline bromide and phenobarbital; G. D. Searle & Co., Post Office Box 5110, Chicago, Ill. 60680 (NDA 7-390).

19. Pamine PB Tablets and Pamine PB Half-Strength Tablets each containing methscopolamine bromide and phenobarbital; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002 NDA 8-942).

20. Pamine PB Drops containing methscopolamine bromide and phenobarbital; The Upjohn Co. (NDA 9-260).

21. Pamine PB Elixir containing methscopolamine bromide and phenobarbital; The Upjohn Co. (NDA 9-261).

22. Daricon PB Tablets containing oxyphencyclimine hydrochloride and phenobarbital; Pfizer Laboratories Division, Pfizer, Inc., 235 East 42d Street, New York, N.Y. 10017 (NDA 13-515).

23. Tral with Phenobarbital Tablets containing hexocyclium methylsulfate and phenobarbital; Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064 (NDA 10-599).

24. Tral with Phenobarbital Gradumet, Sustained Release Tablets containing hexocyclium methylsulfate and phenobarbital; Abbott Laboratories (NDA 11-200).

25. Pathilon with Phenobarbital Sequels (Sustained Release Capsules) containing tridihexethyl chloride and phenobarbital; Lederle Laboratories Division, American Cyanamid Co., Pearl River, N.Y. 10965 (NDA 11-940).

26. Pro-Banthine with Phenobarbital Tablets and Probital Tablets each containing propantheline bromide and phenobarbital; G. D. Searle & Co. (NDA 9-014).

27. Monomeb Tablets containing penthienate bromide and mephobarbital; Winthrop Laboratories, 90 Park Avenue, New York, N.Y. 10016 (NDA 9-032).

28. Trocinate with Phenobarbital Tablets containing thiphenamil hydrochloride and phenobarbital; Wm. P. Poythress and Co., Inc., 16 North 22d Street, Richmond, Va. 23217 (NDA 6-098).

29. Metropine with Phenobarbital Tablets containing methylatropine nitrate and phenobarbital; Strasenburgh Laboratories, Division Wallace and Tiernan, Inc., 755 Jefferson Road, Rochester, N.Y. 14623 (NDA 4-298).

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. These drugs lack substantial evidence of effectiveness if labeled for use in gastritis; duodenitis; aerophagia; biliary tract diseases (cholelithiasas, cholecystitis, and biliary dyskinesia); or chronic pancreatitis.

2. These drugs are possibly effective for their other labeled indications.

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 a drug labeled with those indications described 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. 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. 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 each firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 597, 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: July 7, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11623 Filed 7-26-72;8:48 am]

[DESI 2847]

CERTAIN INJECTABLE MULTIPLE VITAMIN PREPARATIONS

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 drugs for parenteral use:

1. Breonex L Injectable, and;

2. Breonex M Injectable, both containing thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, dexpyridoxine hydrochloride, and cyanocobalamin; Tilden Yates Laboratories, Inc., Fairfield Road, Wayne, NJ 07470 (NDA 2-847).

3. Beclysyl Injectable containing dextrose, sodium chloride, thiamine hydrochloride, riboflavin, niacinamide, pridoxine hydrochloride, and cyanocobalamin; Abbott Laboratories, Inc., 14th and Sheridan Road, North Chicago, IL 60064 (NDA 4-635).

4. Parbexin Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, riboflavin, and pyridoxine hydrochloride; Smith, Miller & Patch, Inc., 401 Joyce Kilmer Avenue, New Brunswick, NJ 08902 (NDA 4-895).

5. Berocca—C Injectable, and;

6. Berocca—C 500 Injectable, both containing thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, d-biotin, and ascorbic acid; Roche Laboratories, Division of Hoffman LaRoche Inc., Roche Park, Nutley, N.J. 07110 (NDA 6-071).

7. Folbesyn Injectable containing thiamine hydrochloride, sodium panthothenate, niacinamide, riboflavin, pyridoxine, cyanocobalamin, ascorbic acid, and folic acid; Lederle Laboratories, Division of American Cyanamid Co., Post Office Box 500, Pearl River, NY 10965 (NDA 6-141).

8. Vi-Syneral Injectable containing vitamin A, ergocalciferol, ascorbic acid, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, dl-alpha tocopheryl acetate; USV Pharmaceuticals Corp., 1 Scarsdale Road, Tuckahoe, NY 10707 (NDA 6-373).

9. Manibee Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, pyridoxine hydrochloride, and riboflavin; and;

10. Manibee—C 500 Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, pyridoxine hydrochloride, riboflavin, and ascorbic acid; Endo Laboratories, Inc., 1000 Stewart Avenue, Garden City, NY 11530 (NDA 7-590).

11. Betolake Improved Injectable containing thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, and dexpanthenol; Lakeside Laboratories, Inc., 1707 East North Avenue, Milwaukee, WI 53201 (NDA 7-619).

12. M.V.I. Injectable containing ascorbic acid, vitamin A, ergocalciferol, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, and dl-alpha tocopheryl acetate; U.S.V. Pharmaceutical Corp. (NDA 8-809).

13. Soluzyme Injectable containing cyanocobalamin, floic acid, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, sodium pantothenate, and niacinamide; The Upjohn Co., 7171 Portage Road, Kalamazoo, MI 49002 (NDA 7-094).

The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that there is a lack of substantial evidence, within the meaning of the Federal Food, Drug, and Cosmetic Act, that these drugs, as currently formulated, will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling since they lack certain essential vitamins and some have vitamins present in too high or too low a dose.

Accordingly, the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the above-listed new drug applications. Any related drug for human use, not the subject of an approved new drug application, may be affected by this action.

Prior to initiating such action, however, the Commissioner invites the holders of the new drug applications for these drugs and any interested persons who might be adversely affected by their removal from the market, to submit pertinent data bearing on the proposal within 30 days after publication hereof in the FEDERAL REGISTER.

To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well-organized, and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in section 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 the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

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 2847, 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 authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 7, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

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[DESI 2238; Docket No. FDC-D-500; NDA 4-040 etc.]

CERTAIN PREPARATIONS FOR VAGINAL USE

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 groups of drugs:

GROUP A

1. Gentia-Jel containing gentian violet; marketed by Westwood Pharmaceuticals, Inc., 468 DeWitt St., Buffalo, N.Y. 14213 (NDA 5-850).

GROUP B

1. Cortril Vaginal Tablets containing hydrocortisone; marketed by Pfizer Laboratories, Div. Pfizer & Co., Inc., 235 East 42nd St., New York, N.Y. 10012 (NDA 9-796).

GROUP C

1. Negatan Solution containing negatol; marketed by Eli Lilly and Co., 740 S. Alabama St., Indianapolis, Ind. 46206 (NDA 2-238).

GROUP D

1. Premarin Cream containing conjugated estrogens; marketed by Ayerst Laboratories Div. of American Home Products Corp., 685 Third Ave., New York, N.Y. 10017 (NDA 5-900).

2. Diethylstilbestrol Suppositories (Vaginal); marketed by Eli Lilly and Co. (NDA 4-040).

3. Dienestrol Cream marketed by Ortho Pharmaceutical Corp. Div. Johnson and Johnson, Route 202, Raritan, N.J. 08869 (NDA 6-110).

GROUP E

1. Sterisil Vaginal Gel containing hexetidine; formerly marketed by Warner-Chilcott Laboratories, Div. Warner-Lambert Pharmaceutical Co., 201 Tabor Rd., Morris Plains, N.J. 07950 (NDA 10-189, NDA approval withdrawn October 14, 1971 (36 F.R. 19995)).

2. Sultrin Cream containing sulfathiazole, sulfacetamide, benzoylsulfanilamide, and urea; marketed by Ortho Pharmaceutical Corp. (NDA 5-794).

3. Gantrisin Cream containing sulfisoxazole; marketed by Roche Laboratories, Div. Hoffmann-LaRoche, Inc., Roche Park, Nutley, N.J. 07110 (NDA 9-173).

4. Westhiazole Vaginal containing sulfathiazole; marketed by Westwood Pharmaceuticals, Inc. (NDA 5-514).

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 drugs 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. The drug in Group A above is effective in the treatment of vulvovaginal candidiasis.

2. The drug in Group B above is:

a. Effective for chemical or allergic vulvovaginitis;

b. Lacking substantial evidence of effectiveness when labeled for the treatment or as an adjunct to the treatment of all types of vaginitis; and

c. Possibly effective for its other labeled indications.

3. The drug in Group C above is:

a. Effective as a styptic (astringent and hemostatic) and

b. Possibly effective for its other labeled indications.

4. The drugs in Group D above are:

a. Effective in the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases;

b. Possibly effective when labeled for the treatment of acne vulgaris; and

c. Lacking substantial evidence of effectiveness if labeled for mammary mypoplasia.

5. The drugs in Group E above are:

a. Effective for *Haemophilus vaginalis* vaginitis;

b. Probably effective as deodorants for saprophytic infection after radiation therapy;

c. Lacking substantial evidence of effectiveness for cervicitis, cervical infections, or infections due to or secondary to trichomonas or candida; and

d. Possibly effective for their other labeled indications.

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 preparations are in cream, gel, tablet, solution, suppository or suspension form suitable for vaginal and/or topical 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 the labeling bears adequate information for safe and effective use of the drugs. The effective and probably effective indications are as follows:

GROUP A

Gentian violet is indicated for the treatment of vulvovaginal candidiasis.

GROUP B

Hydrocortisone vaginal tablets are indicated for chemical or allergic vulvovaginitis.

GROUP C

Negatol solution is indicated for use as a styptic (astringent and hemostatic).

GROUP D

(*Name of drug*) is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

GROUP E

(*Name of drug*) is indicated for treatment of *Haemophilus vaginalis* vaginitis. It may also be used as a deodorant for saprophytic infection following radiation therapy.

c. Labeling for preparations containing diethylstilbestrol or dienestrol should include the following:

CONTRAINDICATIONS

A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy.

d. Labeling for preparations containing conjugated estrogens should include the following:

WARNING

A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

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, and, for drugs in Group E, the submission of adequate data to show the biologic availability of the drug in the formulation which is

marketed, as described in paragraph (a)(1)(ii) of that notice. 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 for a drug in Groups A through D, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice, or for a drug in Group E, 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 2238, 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: July 14, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

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[DESI 7519]

CERTAIN ORAL MERCURIAL DIURETICS

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 mercurial diuretic drugs for oral use:

1. Cumertilin Tablets containing mercumatilin; Endo Laboratories, Inc., 1000 Stewart Ave., Garden City, N.Y. 11530 (NDA 7-519).

2. Neohydrin Tablets containing chlormerodrin; Lakeside Laboratories, Div. Colgate-Palmolive Co., 1707 East North Ave., Milwaukee, Wis. 53202 (NDA 8-406).

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.a. Mercumatilin administered orally is probably effective for its labeled indications as a diuretic for treatment of edema in cardiac insufficiency; nephrotic syndrome; ascites of liver disease and other conditions where marked diuresis is indicated; and ACTH, cortisone, or phenylbutazone-induced edema.

b. The drug is possibly effective for use in cardiac dyspnea.

c. The drug lacks substantial evidence of effectiveness in periodic premenstrual edema and obesity with salt and water retention.

2.a. Chlormerodrin administered orally is probably effective for its recommended use in congestive heart failure.

b. It is possibly effective for use in recurring edema and ascites; polyhydramnios; Meniere's syndrome; arteriosclerotic heart disease; hypertensive heart disease; preeclampsia; toxemia; and cardiac dyspnea and asthma.

c. The drug lacks substantial evidence of effectiveness for use in the treatment of migraine headache, premenstrual tension, and fluid retention masked by obesity.

B. *Marketing status.* 1. Within 60 days of the date of publication of this announcement in the FEDERAL REGISTER, the holder of any previously approved new drug application for a drug which 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 and which contains an "Indications" section in accord with that described below. Such 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 delete such indications and to put the revised labeling into use within 60 days after the date of publication thereof in the FEDERAL REGISTER may be sult 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 to delete all claims for which substantial evidence of effectiveness is lacking as described in paragraph A above and to be