

March 28

guaranteed resolving power of this stage is 8 angstroms. (The lower the numerical rating in terms of angstrom units, the better the resolving power.) We are advised by the Department of Health, Education, and Welfare in its memorandum dated December 17, 1971, that the guaranteed resolving power of the tilt stage of the foreign article is pertinent to the applicant's research studies. We, therefore, find that the Model EMU-4C electron microscope is not of equivalent scientific value to the foreign article for such purposes as this article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article for the purposes for which such article is intended to be used, which is being manufactured in the United States.

SETH M. BODNER,
Director,
Office of Import Programs.

[FR Doc. 72-4678 Filed 3-27-72; 8:51 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. FDC-D-444; NDA No. 12-658]

ARMOUR PHARMACEUTICAL CO.

Hydroxyphenamate; Notice of Withdrawal of Approval of New-Drug Application

In the FEDERAL REGISTER of June 25, 1970 (35 F.R. 10394), the Commissioner of Food and Drugs announced (DESI 6566) his conclusions pursuant to evaluation of a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, concerning the following drug:

NDA 12-658; Listica Tablets, containing hydroxyphenamate; Armour Pharmaceutical Co., Box 511, Kankakee, Ill. 60901.

The announcement stated that the drug was regarded as either lacking substantial evidence of effectiveness or possibly effective for the various labeled indications. Six months from the date of that publication were allowed for the holder of the application and any person marketing such drug without approval to obtain and submit data providing substantial evidence of effectiveness of the drug for the possibly effective indications. No such data have been received and the holder of said new-drug application has requested withdrawal of approval of its new-drug application and thereby has waived opportunity for a hearing, stating that marketing of the drug was discontinued in 1971.

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 305(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under authority delegated to him (21 CFR 2.120), finds

that on the basis of new information before him with respect to said drug, evaluated together with the evidence available to him when the application was approved, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing finding, approval of new-drug application No. 12-658, and all amendments and supplements thereto, is withdrawn effective on the date of publication hereof in the FEDERAL REGISTER (3-28-72).

Dated: March 16, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 72-4689 Filed 3-27-72; 8:53 am]

[DESI 4054-4]

CERTAIN SHORT-ACTING AND INTERMEDIATE-ACTING SYSTEMIC SULFONAMIDES

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration published announcements in the FEDERAL REGISTER June 17, 1969 (34 F.R. 9464), August 30, 1969 (34 F.R. 13948), and November 28, 1970 (35 F.R. 18215), regarding the efficacy of certain short-acting and intermediate-acting systemic sulfonamides.

The notices stated that certain preparations containing sulfachlorpyridazine; sulfadiazine; sulfaethidole; sulfamerazine; sulfamethizole; sulfamethoxazole; sulfisomidine; sulfisoxazole; or sulfadiazine and sulfamerazine with or without sulfamethazine were regarded as effective, probably effective, possibly effective, and/or lacking substantial evidence of effectiveness for their various labeled indications.

Based on a further reevaluation of the reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, and other available evidence, the Commissioner of Food and Drugs finds it appropriate to amend the announcement of November 28, 1970 (35 F.R. 18215) by:

1. Reclassifying sulfisoxazole, sulfamethoxazole, sulfisomidine, sulfachlorpyridazine, sulfaethidole, sulfamethizole, and combinations of sulfadiazine, sulfamerazine, and sulfamethazine from probably effective to effective in the treatment of recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis, and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Aerobacter*, staphylococcus, *Proteus mirabilis*, and less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

2. Reclassifying the following probably effective indication for sulfonamides other than sulfadiazine as lacking substantial evidence of effectiveness in that no new evidence of effectiveness has been

received pursuant to the notices of August 30, 1969, and November 28, 1970: For use in the prophylaxis of rheumatic fever as an alternative to penicillin.

3. Reclassifying the possibly effective indications as lacking substantial evidence of effectiveness in that no new evidence of effectiveness has been received pursuant to the notices of August 30, 1969, and November 28, 1970, i.e.; the treatment of pneumococcal infections; gas gangrene; lymphogranuloma venereum; shigellosis; for suppressive therapy in patients with indwelling catheters, ureterostomies, urinary stasis, cord bladder, and before and after genitourinary surgery and instrumentation; and in "acute or chronic otitis media." Sulfachlorpyridazine, sulfaethidole, sulfamethizole, and sulfamethoxazole are, for the same reason, reclassified as lacking substantial evidence of effectiveness in the treatment of meningococcal meningitis and as adjunctive therapy in *Haemophilus influenzae* meningitis.

4. Adding information under the "Adverse Reactions" section relating to the goitrogenic effects of sulfonamides during long-term administration in the rat.

5. Rewording the "Indications" and "Adverse Reactions" sections to reflect the above findings, as follows:

INDICATIONS

Chancroid.
Trachoma.
Inclusion conjunctivitis.
Nocardiosis.

Acute urinary tract infections (primarily pyelonephritis, pyelitis, and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Aerobacter*, staphylococcus, *Proteus mirabilis*, and less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

Toxoplasmosis as adjunctive therapy with pyrimethamine.

Malaria due to chloroquine-resistant strains of *Plasmodium falciparum*, when used as adjunctive therapy.

Meningococcal meningitis prophylaxis when sulfonamide-sensitive group A strains are known to prevail in family groups or larger closed populations. (The prophylactic usefulness of sulfonamides when group B or C infections are prevalent is not proven and in closed population groups may be harmful.)

In acute otitis media due to *Haemophilus influenzae* when used concomitantly with adequate doses of penicillin.

Add for: Sulfisoxazole, sulfamethoxazole, sulfisomidine, sulfachlorpyridazine, sulfaethidole, sulfamethizole, and combinations of sulfadiazine, sulfamerazine, and sulfamethazine only—The treatment of recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually, *E. coli*, *Klebsiella-Aerobacter*, staphylococcus, *Proteus mirabilis*, and less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

Add for: Sulfadiazine only—Prophylaxis against recurrences of rheumatic fever as an alternative to penicillin.

Add for: Sulfadiazine, sulfamerazine, sulfisomidine, sulfisoxazole, and combinations of sulfadiazine and sulfamerazine with or without sulfamethazine only—

Haemophilus influenzae meningitis (as adjunctive therapy with parenteral streptomycin), and

Meningococcal meningitis (where the organism has been demonstrated to be susceptible).

Important note. *In vitro* sulfonamide sensitivity tests are not always reliable. The test must be carefully coordinated with bacteriologic and clinical response. When the patient is already taking sulfonamides, followup cultures should have aminobenzotic acid added to the culture media.

Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of antibacterial agents including the sulfonamides, especially in the treatment of chronic and recurrent urinary tract infections.

Wide variation in blood levels may result with identical doses. Blood levels should be measured in patients receiving sulfonamides for serious infections. Free sulfonamide blood levels of 5-15 mg. per 100 ml. may be considered therapeutically effective for most infections, with blood levels of 12-15 mg. per 100 ml. optimal for serious infections; 20 mg. per 100 ml. should be the maximum total sulfonamide level, as adverse reactions occur more frequently above this level.

ADVERSE REACTIONS

Blood dyscrasias. Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

Allergic reactions. Erythema multiforme (Stevens-Johnson Syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis.

Gastrointestinal reactions. Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. reactions. Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

Miscellaneous reactions. Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarthritis nodosum and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

6. Revising the first paragraph of the Warnings section (that follows "Use in Pregnancy") so that the entire section reads as follows:

WARNINGS

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever and glomerulonephritis.

Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, and other blood dyscrasias.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice

may be early indications of serious blood disorders.

Complete blood counts should be done frequently in patients receiving sulfonamides.

The frequency of renal complications is considerably lower in patients receiving the more soluble sulfonamides. Urinalysis with careful microscopic examinations should be obtained frequently in patients receiving sulfonamides.

7. Adding a statement in the Precautions section so that the section reads as follows:

PRECAUTIONS

Sulfonamides should be given with caution to patients with impaired renal or hepatic function and to those with severe allergy or bronchial asthma.

Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

The new-drug applications held by Parke, Davis & Co. (NDA 4-154), Abbott Laboratories (NDA 4-125), Ayerst Laboratories (NDA 8-565), Ciba Pharmaceutical Co. (NDA 8-070) and Roche Laboratories (NDA's 6-525, 6-917, 9-182 and 12-715) have been satisfactorily supplemented to delete those claims for which substantial evidence of effectiveness is lacking and to be in accord with this notice.

Other holders of applications approved for these drugs should submit, within 60 days following publication of this amended announcement in the FEDERAL REGISTER, supplements to their new-drug applications to provide for revised labeling in accord with the sections above. Such supplements 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 time.

Any such preparation, for human use, introduced into interstate commerce after 60 days following publication of this notice in the FEDERAL REGISTER with labeling bearing indications that lack substantial evidence of effectiveness may be subject to regulatory proceedings.

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: March 16, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 72-4684 Filed 3-27-72; 8:53 am]

[DESI 7322]

DOXYCYCLINE FOR ORAL USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration published an announcement in the FEDERAL REGISTER of September 2, 1970 (35

F.R. 13897), regarding the efficacy of tetracycline, oxytetracycline, chlortetracycline, demethylchlortetracycline, and rolitetracycline for systemic use. A correction of that announcement, which extended the labeling guidelines for tetracycline to include doxycycline capsules and suspension and methacycline capsules and syrup, was published April 20, 1971 (36 F.R. 7473). Based upon new information and a reevaluation of available data, the Commissioner of Food and Drugs finds it appropriate to amend the labeling section of the September 2, 1970 and April 20, 1971 announcements insofar as they concern doxycycline as follows: (Revised labeling for tetracycline, oxytetracycline, chlortetracycline, demeclocycline, rolitetracycline, and methacycline is the subject of a separate notice.)

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

Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms.

The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Microorganisms may be considered susceptible if the M.I.C. (minimum inhibitory concentration) is not more than 4.0 mcg./ml. and intermediate if the M.I.C. is 4.0 to 12.5 mcg./ml.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg. tetracycline disc should give a zone of at least 19 mm. when tested against a tetracycline-susceptible bacterial strain.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg. dose, normal adult volunteers averaged peak serum levels of 2.6 mcg./ml. of doxycycline at 2 hours decreasing to 1.45 mcg./ml. at 24 hours. Excretion of doxycycline by the kidney is about 40 percent/72 hours in individuals with normal function (creatinine clearance about 75 ml./min.). This percentage excretion may fall as low as 1-5 percent/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml./min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

INDICATIONS

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsialpox and tick fevers),

Mycoplasma pneumoniae (PPLO, Eaton Agent),

Agents of psittacosis and ornithosis, Agents of lymphogranuloma venereum and granuloma inguinale,