83900-S5

NDA 83-500/S-005

Smith Kline & French Laboratories
Attention: J.F. Cassin
1500 Spring Garden Street
P.O. Box 7929
Philadelphia, PA 19101

Gentlemen:

Reference is made to your supplement dated December 20, 1978 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Benzedrine (Amphetamine Sulfate) Tablets, 5 mg. and 10 mg.

The supplemental application provides for revised package insert (BZ:L19) dated November 1978.

We have completed the review of this supplemental application and it is approved. Our letter of February 26, 1976 detailed the conditions relating to the approval of this application.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 12/11/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

PHI-DO DUP HFD-616 HFD-530
HBehrens (HFD-530)
HBehrens/MSeife
ft/mlb/12/5/80 approved
1042E

H.T.B.
2/10/81

REVIEW OF SUPPLEMENT

DATE COMPLETED: 9-17-79 ANDA #: 83-900/S-005
S-006

CO. NAME: Smith Kline & French Labs.
Philadelphia, PA 19101

NAME OF DRUG: Trade: Benzedrine Tablets

Generic: Amphetamine Sulfate Tablets

DATE OF SUBMISSION: S-005 12-20-78 Labeling revision
S-006 2-6-79 Labeling revision

TYPE OF SUBMISSION: Supplement - name distributor

CLINICAL EVALUATION:

1. Container labels: Satisfactory
S-006 10 mg. tablets bottles of 100

2. Insert labeling: Satisfactory
date: Nov. 78 S-005

CONCLUSION: Labeling is satisfactory for the safe and effective use of this product.

RECOMMENDATIONS: Approve supplements S-005, S-006.
S-008

/S/
V.V. Karusaitis, M.D.

cc:dup
VVK/wlh/9-18-79

S-008 12-14-79 Labeling Revision
5MG Tablets Bottle of 100 Suspension

SK&F
a SmithKline company

SMITH KLINE &FRENCH LABORATORIES

1500 Spring Garden St., P.O. Box 7929, Philadelphia, PA 19101 • 215-854-4000

cable SMITHKLINE PHILADELPHIAPA
telex 83-4487

December 20, 1978

NDA 83-900
'Benzedrine' Tablets

Docket No. 78N-0278

NDA NO. 83-900 REF. NO. 1005
NDA SUPPL FOR Labeling Rev
FPL

Special new drug application
Supplement - changes being effected

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs, HFD #530
Document Control Room #16-72
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

In accordance with 314.8 (d)(e), I have enclosed 12 final printed copies of the package insert (BZ:L19) for 'Benzedrine' (brand of amphetamine sulfate) revised to conform to the Federal Register of October 24, 1978 ("Uniform Physician Labeling for Stimulant Drugs for Children"). The previous insert (BZ:L18) was never used in a production run.

This labeling will be placed in use early in February, 1979.

Sincerely yours,

J.F. McEntee for

J.F. Cassin
Manager, Regulatory Affairs

JFC/jh
Enclosures

BZ:L19

PRESCRIBING INFORMATION

DATE OF ISSUANCE NOV. 1978

Benzedrine®

brand of **amphetamine sulfate**

Spansule® capsules

brand of sustained release capsules

and Tablets

WARNING

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. THEY SHOULD THUS BE TRIED ONLY IN WEIGHT REDUCTION PROGRAMS FOR PATIENTS IN WHOM ALTERNATIVE THERAPY HAS BEEN INEFFECTIVE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME IN OBESITY MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION

Benzedrine (amphetamine sulfate, SK&F) is a racemic mixture of the dextro and levo isomers of amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, amphetamine is *dl*-alpha-methylphenethylamine, and is present in all forms of 'Benzedrine' as the neutral sulfate.

Spansule® sustained release capsules—Each 'Spansule' sustained release capsule contains amphetamine sulfate, 15 mg., so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period.

Tablets—Each tablet contains amphetamine sulfate, 5 mg. or 10 mg.

ACTIONS

Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics." It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anorectic" drugs lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The origins of the increased weight loss due to the various possible drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and nondrug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks' duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

'Benzedrine' *Spansule* capsules are formulated to release the active drug substance *in vivo* in a more gradual fashion than the standard formulation, as demonstrated by blood levels. The formulation has not been shown superior in effectiveness over the same dosage of the standard, noncontrolled-release formulations given in divided doses.

INDICATIONS

Benzedrine (amphetamine sulfate, SK&F) is indicated:

1. **In Narcolepsy.**
2. As an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children terized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.
3. **In Exogenous Obesity,** as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients refractory to alternative therapy, e.g., repeated diets, group programs, and other drugs. The limited usefulness of amphetamines (see ACTIONS) should be weighed against possible risks inherent in use of the drug, such as those described below.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

When tolerance to the "anorectic" effect develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Dependence: Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.

Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

in

pregnancy has not been established. Reproduction studies in mammals at high multiples of the human dose have suggested both an embyrotoxic and teratogenic potential. Use of amphetamines by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and infant.

Usage in Children: Amphetamines are not recommended for use as anorectic agents in children under 12 years of age, or in children under 3 years of age with the behavioral syndrome described under INDICATIONS.

Clinical experience suggests that in psychotic children, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of amphetamines may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS

Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen.

Amphetamines may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Drug treatment is not indicated in all cases of the behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

Long-term effects of amphetamines in children have not been well established.

ADVERSE REACTIONS

Cardiovascular: Palpitation, tachycardia, elevation of blood pressure. *Central nervous system:* Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

DOSAGE AND ADMINISTRATION

Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses—particularly with the 'Spansule' capsule form—should be avoided because of the resulting insomnia.

Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, Benzedrine (amphetamine sulfate, SK&F) may be used. The suggested initial dose for patients aged 6-12 is 5 mg. daily; daily dose may be raised in increments of 5 mg. at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg. daily; daily dosage may be raised in increments of 10 mg. at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. 'Spansule' capsules may be used for once-a-day dosage wherever appropriate. With tablets, give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Behavioral Syndrome in Children: Not recommended for children under 3 years of age.

In children from 3 to 5 years of age, start with 2.5 mg. daily; daily dosage may be raised in increments of 2.5 mg. at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg. once or twice daily; daily dosage may be raised in increments of 5 mg. at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.

'Spansule' capsules may be used for once-a-day dosage wherever appropriate.

With tablets, give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Exogenous Obesity: Usual dosage is one 15 mg. 'Spansule' capsule—or 2 if required—daily, taken in the morning, or up to 30 mg. daily by tablets, taken in divided doses of 5 to 10 mg. 30 to 60 minutes before meals. Not recommended for this use in children under 12 years of age.

OVERDOSAGE

SYMPTOMS—Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

TREATMENT—Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Since much of the 'Spansule' capsule medication is coated for gradual release, therapy directed at reversing the effects of the ingested drug and at supporting the patient should be continued for as long as overdosage symptoms remain. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

HOW SUPPLIED

'Spansule' capsules—15 mg., in bottles of 50. **Tablets**—5 mg. and 10 mg., in bottles of 100.

Smith Kline &French Laboratories
Division of SmithKline Corp.
Philadelphia, Pa. 19101

Printed in U.S.A. BZ:L19.