CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

Approval Letter

-299

MAY 13 1999

Endo Pharmaceuticals, Inc.
Attention: Carol Patterson
500 Endo Boulevard
Garden City, NY 11530

Dear Madam:

This is in reference to your abbreviated new drug application dated February 27, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dextroamphetamine Sulfate Tablets USP, 5 mg.

Reference is also made to your amendments dated April 23, and August 13, 1998; and March 13, April 27, and April 30, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dextroamphetamine Sulfate Tablets USP, 5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dexedrine® Tablets, 5 mg, of Smithkline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

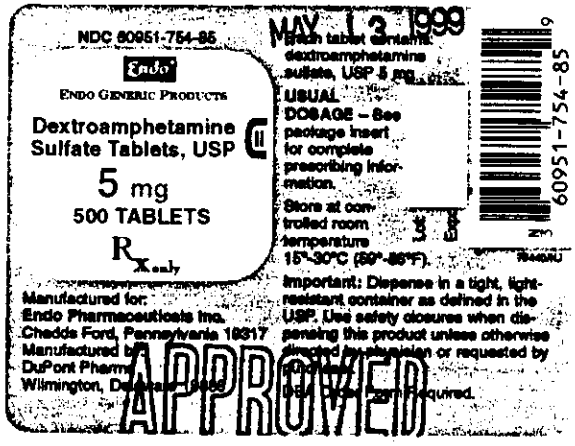
/S/ -/13/99

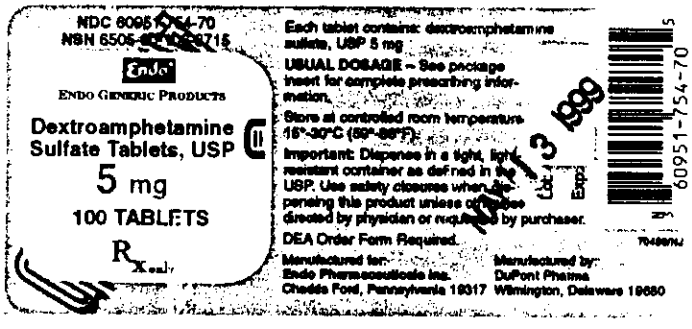
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

FINAL PRINTED LABELING


NDC 60951-754-85
Endo
ENDO GENERIC PRODUCTS
Dextroamphetamine Sulfate Tablets, USP
5 mg
500 TABLETS
Rx only
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317
Manufactured by
DuPont Pharm
Wilmington, De
MAY 13 1999
Each tablet contains: dextroamphetamine sulfate, USP 5 mg.
USUAL DOSAGE – See package insert for complete prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
Important: Dispense in a tight, light-resistant container as defined in the USP. Use safety closures when dispensing this product unless otherwise directed by physician or requested by
Rx Only
Exp
60951-754-85
APPROVED


NDC 60951-754-70
NSN 6505-00-109-9715
Endo
ENDO GENERIC PRODUCTS
Dextroamphetamine Sulfate Tablets, USP
C II
5 mg
100 TABLETS
Rx only
Each tablet contains: dextroamphetamine sulfate, USP 5 mg.
USUAL DOSAGE – See package insert for complete prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
Important: Dispense in a light, light-resistant container as defined in the USP. Use safety closures when dispensing this product unless otherwise directed by physician or required by purchaser.
DEA Order Form Required.
Lot 13
1999
Exp
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317
Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880
70469NJ
60951-754-70

Endo

ENDO GENERIC PRODUCTS

Dextroamphetamine Sulfate Tablets, USP

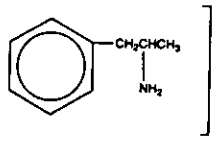
C II

WARNING

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME 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

Dextroamphetamine sulfate is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is (+)-α-methylphenethylamine sulfate (2:1), and is present in all forms of dextroamphetamine sulfate as the neutral sulfate. The molecular formula is $(C_9H_{13}N)_2.H_2SO_4$; and the molecular weight is 368.50. The structural formula is as follows:



Each tablet, for oral administration, contains dextroamphetamine sulfate, 5 mg and the following inactive ingredients: colloidal silicon dioxide, confectioner's sugar, corn starch, lactose monohydrate, and magnesium stearate.

CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine, sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevations of systolic and diastolic blood pressures 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.

Pharmacokinetics:

The single ingestion of two 5 mg tablets by healthy volunteers produced an average peak dextroamphetamine blood level of 29.2 ng/mL at 2 hours post-administration. The average half-life was 10.25 hours. The average urinary recovery was 45% in 48 hours.

INDICATIONS AND USAGE

Dextroamphetamine sulfate tablets are indicated:

1. In Narcolepsy.

2. In Attention Deficit Disorder with Hyperactivity, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in pediatric patients (ages 3 years to 16 years) with a behavioral syndrome characterized 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.

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).

PRECAUTIONS

General:

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

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

DEXTROAMPHETAMINE SULFATE TABLETS, USP 6511-00

DEXTROAMPHETAMINE SULFATE TABLETS, USP 6511-00

Information for Patients:
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 Interactions:
Acidifying agents–Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers–Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents–Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic–Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors–MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines–Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives–Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine–Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide–Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol–Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate–The stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine–Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy–Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine–Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital–Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin–Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene–In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids–Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:
- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis:
Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of dextroamphetamine sulfate tablets have not been performed.

Pregnancy–Teratogenic Effects:
Pregnancy Category C. Dextroamphetamine sulfate tablets have been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (Vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Dextroamphetamine sulfate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:
Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Nursing Mothers:
Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use:
Long-term effects of amphetamines in pediatric patients have not been well established.

Amphetamines are not recommended for use in pediatric patients under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

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

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

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

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity 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.

ADVERSE REACTIONS

Cardiovascular:
Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System:
Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal:
Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Dextroamphetamine sulfate is a Schedule II controlled substance.

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. This is rare with oral amphetamines.

OVERDOSAGE

Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, 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:
Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

DOSAGE AND ADMINISTRATION
Amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Narcolepsy:
Usual dose 5 to 60 mg 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, dextroamphetamine sulfate tablets may be used. The suggested initial dose for patients aged 6 to 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. Give the first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Attention Deficit Disorder with Hyperactivity:
Not recommended for pediatric patients under 3 years of age.

In pediatric patients 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 pediatric patients 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 mg per day.

Give the 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.

HOW SUPPLIED
Dextroamphetamine Sulfate Tablets, USP are supplied as 5 mg white, capsule-shaped biconvex tablets, bisected on one side, and embossed with "E754" on the other as follows:

Bottles of 100	NDC 60951-754-70
Bottles of 500	NDC 60951-754-85

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container, with a child-resistant closure (as required). Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

R_{only}

DEA Order Form Required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Endo

Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

CHEMISTRY REVIEW(S)

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemist Review 2/22/99

#38

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-299

3. NAME AND ADDRESS OF APPLICANT
Endo Pharmaceutical Inc.
Attention: Carol Patterson
500 Endo Blvd.
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is the referenced listed drug Dexedrine Tablets 5 mg manufactured by Smith Kline Beecham Pharmaceuticals.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Dextroamphetamine Sulfate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Submission	02/27/98
Ack. Letter	03/17/98
Amendment	04/23/98
Amendment	08/13/98
Amendment	03/16/99
Amendment	04/27/99

10. PHARMACOLOGICAL CATEGORY
ADDH

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
d-alpha-methylphenethylamine
USP drug substance and drug product

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
03/31/99;04/27/99

Page(s) 12

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemist Review #3

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-299 APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40299 SPONSOR: Endo Pharmaceuticals
DRUG: Dextroamphetamine Sulfate
DOSAGE FORM: Tablet
STRENGTHS/(s): 5 mg
TYPE OF STUDY: Waiver Request
STUDY SITE: Not applicable

STUDY SUMMARY: The waiver of *in vivo* bioequivalence study requirements is granted under 21 CFR 320.22(c).

DISSOLUTION: Not applicable

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: /S/ DATE 5/18/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: SN DATE 5/19/1998

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE 5/21/98

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL:_____ DATE_____

CC:

5/19/98

BIOEQUIVALENCY - ACCEPTABLE

Submission date: Feb. 27, 1998

1. **DISSOLUTION WAIVER** (DIW)

Strengths: 5 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments: Waiver granted

Dextroamphetamine Sulfate
5 mg Tablets
ANDA #40-299
Reviewer: Kuldeep R. Dhariwal
File name: 40299W.298

Endo Pharmaceuticals
500 Endo Boulevard
Garden City,NY 11530
Submission Date:
February 27, 1998

REVIEW OF A DISSOLUTION WAIVER REQUEST

The firm has submitted a waiver request for its dextroamphetamine sulfate, 5 mg tablets. To support the request, the firm has submitted comparative dissolution profiles on its product and reference listed drug, Dexedrine® 5 mg tablets (SmithKline).

Dexedrine® is coded as an AA drug in the therapeutic equivalence evaluation book. Products coded as AA contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate *in vitro* bioequivalence standard that is acceptable to the Agency in order to be approved.

Dexedrine® is indicated in narcolepsy and in attention deficit disorder with hyperactivity.

Formulation: Table 1

Dissolution: Table 2

The firm has used following USP method:

Apparatus:	1 (basket)
Speed:	100 rpm
Medium:	Purified Water
Volume:	500 mL
Sampling times:	15,30,45 and 60 minutes

Comments:

1. The firm has used USP dissolution conditions. However, sample analysis method was changed. The injection volume to . was increased and the detection wavelength was lowered from 254 nm to ım. The method was validated and compared with USP 23 method.

The USP 23 method showed an average of 104.3% of dextroamphetamine sulfate dissolved with a RSD of 1.8%. The alternate method showed an average of 103.5% of dextroamphetamine sulfate dissolved with a RSD of 1.6%.

2. Dissolution data are acceptable. Waiver can be granted.
Tolerance: NLT (Q) in ıinutes

Recommendations:

1. The Division of Bioequivalence agrees that the information submitted by Endo Pharmaceuticals demonstrates that dextroamphetamine sulfate, 5 mg tablets fall under 21 CFR 320.22(c) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Dexedrine® 5 mg tablet manufactured by SmithKline.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug product is dissolved in minutes.

/S/ 5/18/98
Kuldeep R. Dhariwal
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR /S/
FT INITIALED S.NERURKAR /S/ Date 5/19/1998

Concur: Date 5/21/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1

Composition of Dextroamphetamine Sulfate Tablets

Ingredient	mg/tablet
Dextroamphetamine Sulfate,	5.0
Sugar, Confectioners,	
Lactose,	
Corn Starch,	
Colloidal Silicon Dioxide,	
Magnesium Stearate,	
Total	

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Dextroamphetamine Sulfate Tablet
Dose Strength: 5 mg
ANDA No.: 40-299
Firm: Endo Pharmaceuticals
Submission Date: February 27, 1998
File Name: 40299w.298

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium: Water Volume: 500 mL
Specifications: NLT (Q) in minutes
Reference Drug: Dexedrine® Tablet (SmithKline)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #LH 360 Strength(mg) 5			Reference Product Lot #156E19 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	99.0		1.5	61.7		5.7
30	99.1		1.5	86.7		4.7
45	99.3		1.5	97.2		2.1
60	99.4		1.5	99.1		1.4

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-299 APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

:es)

2DV 5/19/98

/98

BIOEQUIVALENCY - ACCEPTABLE

Submission date: Feb. 27, 1998

1. **DISSOLUTION WAIVER** (DIW)

Strengths: 5 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments: Waiver granted

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-299

FIRM: Endo Pharmaceutical Inc.
Attention: Carol Patterson
500 Endo Blvd.
Garden City, NY 11530

DOSAGE FORM: Tablet STRENGTH: 5 mg

DRUG: Dextroamphetamine Sulfate

CGMP STATEMENT/EIR UPDATE STATUS: EER status for drug product manufacturer is acceptable. EER Status for bulk drug supplier is unacceptable due to plant explosion. Grant application approval. Firm will submit prior-approval supplement with required information and qualification data for new supplier subsequent to approval.

BIO STUDY INFORMATION: Bio-waiver requested. Found acceptable 05/18/98.

METHODS VALIDATION: N/A; USP drug substance and drug product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in both container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	SPECIFICATION
Description	
Dissolution	
Assay	

Degradation Products	
Isomeric Purity	and [illegible]

LABELING: Acceptable 11/04/98.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

A copy of the executed batch record for lot #LH360 tabs) begins on p. 221. The instructions follow the blank master record.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The intended production batch size is tablets. The manufacturing process is the same.

RECOMMENDATION: APPROVABLE.

SIGNATURE: /S/ DATE:

[illegible] 4/29/99

ENTS AND COMPOSITION

INGREDIENT	AMT/TAB (MG)	AMT/Exhibit Batch	AMT/Prod. Batch abs
Dextroamphetamine Sulfate	5.0	2.40	20.00
Sugar, Confectioners			
Lactose Spray dried			
Corn Starch			
Colloidal Silicon Dioxide NF			
Magnesium Stearate			
Total			

In-process Testing Blend
Blend Uniformity (mean); RSD NMT

In-process Compression tests
Target Weight:

Hardness:

Thickness:

Friability:

The finished product tests and specifications are as follows:

TEST	SPECIFICATION
Description	
Identification	B
Assay	
Uniformity of Dosage	
Dissolution	
Degradation (HPLC)	%
	%
Isomeric Purity	%

cc:

Endorsements:

/S/

copies 7/21/99

F/T by:ps/4/28/99

v:\firmam\endo\ltrs&rev\40299.apd /S/

/S/

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-299

CORRESPONDENCE

Endo®

Endo Pharmaceuticals Inc.

February 27, 1998

505(j)(ii) a OK
3/11/98
Gregory S. Davis

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Original Abbreviated New Drug Application
Dextroamphetamine Sulfate Tablets, USP, 5 mg

Dear Mr. Sporn:

Pursuant to 21 CFR 314.94 and Section 505(j) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. hereby submits this original Abbreviated New Drug Application (ANDA) for the above-referenced drug product.

This ANDA consists of three volumes submitted in duplicate as archival and technical review copies.

The archival copy of the application consists of three volumes in blue jackets designated as Volumes 1.1 to 1.3. The technical review copy of this application consists of Volumes 1.1 - 1.2 in red jackets (Chemistry, Manufacturing and Controls information and Labeling) and Volume 1.3 (Bioequivalence Waiver and associated documentation) in an orange jacket. In addition, the Methods Validation Package (Section XVIII) has been submitted, in duplicate, in separate black binders.

To assist your review, preceding each volume is the Cover Letter, Table of Contents, ANDA Checklist for Completeness and Acceptability for Filing, and signed Form FDA 3439.

Dextroamphetamine Sulfate Tablets, USP, 5 mg is "AA" rated to the reference listed drug (Dexedrine® 5 mg , manufactured by SmithKline Beecham), as per the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"). Based on this, we have requested a waiver of *in-vivo* bioequivalence studies for this application.

ANDA 40-299

Endo Pharmaceuticals Inc.
Attention: Andrew G. Clair, Ph.D.
500 Endo Blvd.
Garden City, NY 11530

MAR 17 1998

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Dextroamphetamine Sulfate Tablets USP, 5 mg

DATE OF APPLICATION: February 27, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 2, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Gary Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Endo®

Endo Pharmaceuticals Inc.

August 13, 1998

ORIG AMENDMENT
N/A C

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA 40-299; Dextroamphetamine Sulfate Tablets, USP, 5 mg
Major Amendment

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated July 7, 1998 which describes chemistry, manufacturing and controls deficiencies in connection with our original application dated February 27, 1998 for the subject product.

Reference is also made to your facsimile letter dated July 10, 1998 describing labeling deficiencies for the above-referenced file.

In addition, reference is made to my telephone conversation on August 4, 1998 with Kassandra Sherrod, Project Manager, FDA regarding the amendment classification of the subject application.

We are amending the application with our responses to each of your comments in the July 7th and July 10th facsimile letters. Supporting documentation for each response, as required, is enclosed directly behind each response.

Included in this amendment are the following:

1. Completed FDA Form 3439 and Addendum
2. Field Copy Certification
3. A copy of FDA's July 7th and July 10th Facsimile Letters
4. CMC Responses 1-9
5. Final Printed Container Labels and Package Insert and Side-By-Side Comparison

RECEIVED

AUG 14 1998

GENERIC DRUGS

500 ENDO BOULEVARD GARDEN CITY, NY 11530 FAX (516) 832-2291

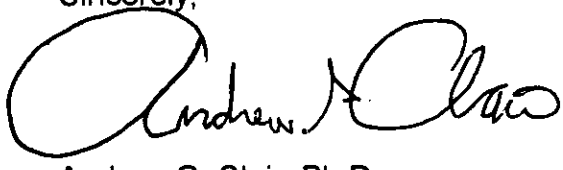
Please note that subsequent to the submission of the original application, we submitted an amendment dated April 23, 1998. This amendment provides for an improved method for the determination of impurities in the drug substance, including degradants, and is stability indicating. Validation of this method was also included in our amendment. Reference is made to our April 23rd amendment in the responses to Comments 2 and 3.

We are disappointed that the April 23rd amendment was not evaluated with the first-cycle review, particularly as it was submitted within 60 days of the initial filing and more than 60 days prior to the date of your deficiency notice. We believe that had the amendment been reviewed in the first cycle, your comments 2 and 3 would have been satisfactorily addressed and the deficiency letter classified as minor rather than major.

We believe that based upon the information provided herein, all outstanding chemistry, manufacturing and controls and labeling issues are addressed and completed. Endo looks forward to an expeditious review of this correspondence and final approval of the subject file.

If there are any questions regarding this amendment, please contact me at (516) 522-3309.

Sincerely,



Andrew G. Clair, Ph.D.
Director, Regulatory Affairs

attachments
ACG:wj
FDADeficResp/Dextro8-10-98.doc

Addendum to Application

Establishment Information
Active Drug Substance:

The manufacturing, packaging and control site for Dextroamphetamine Sulfate USP drug substance is:

Finished Dosage Form:

The manufacturing, packaging and control site of the drug product is:

The manufacturing site is ready for inspection.

The sponsor of this ANDA is:

Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

DMF Cross References (from the original application)

Drug Substance:

Packaging Components:

Bottle
Bottle
Bottle resin
Bottle colorant
Bottle colorant

:er
ant

Endo®

Endo Pharmaceuticals Inc.

April 27, 1999

FA

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA 40-299; Dextroamphetamine Sulfate Tablets, USP, 5 mg
Telephone Amendment

Dear Mr. Sporn:

Reference is made to the telephone conversation yesterday between Mr. Andrew Lanowski, FDA reviewer and Carol Patterson, Endo Pharmaceutical Inc. with regards to the above mentioned application.

In the March 16, 1999 amendment, as per FDA's request, we committed to performing blend uniformity on commercial batches using a specification of The revision was incorporated on page 284.

Mr. Lanowski has requested that we also revise page 279 of the original ANDA to reflect this commitment. In addition, he requested that the limit be specific for the mean of the individual tablets.

Included in this amendment are revised pages 279 and 284 of the original ANDA which now reflects our commitment to perform blend uniformity on all commercial batches with the following specific limit:

(mean of individual test results) with an RSD of NMT

500 ENDO BOULEVARD GARDEN CITY, NY 11530 FAX (516) 832-2291

This response completes the only outstanding issue for this ANDA. If there any further questions, please call me at (516) 522-3305. We anxiously await the approval of this ANDA.

Sincerely,

Carol Patterson, MS
Manager, Regulatory Affairs

attachments
CAP:wj
FDA-1999.doc

Endo®

Endo Pharmaceuticals Inc.

March 16, 1999

NEW CORRESP
NC to
Fax

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA 40-299; Dextroamphetamine Sulfate Tablets, USP, 5 mg
FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to your February 22, 1999 facsimile correspondence which describes chemistry, manufacturing and controls deficiencies for the subject file.

We are amending the application with our responses to each of the Agency's comments. Included in this amendment are the following:

- FDA Form 356h and Addendum
- Field Copy Certification
- A copy of FDA's February 22, 1999 Facsimile Letter
- CMC Responses

It is our understanding that this amendment resolves all outstanding issues, and we look forward to approval of this application.

If there are any questions regarding this information, please contact me at (516) 522-3306.

Sincerely,

Jeanne Stelter

Jeanne Stelter
Regulatory Associate

RECEIVED
MAR 17 1999
GENERIC DRUGS

attachments

500 ENDO BOULEVARD GARDEN CITY, NY 11530 FAX (516) 832-2291

In support of this request we are providing test results including dissolution testing of the finished product and comparative dissolution data of Endo's product versus the Reference Listed Drug which indicate that this product meets *in-vitro* dissolution requirements.

Endo Pharmaceuticals Inc. certifies that a copy of the chemistry, manufacturing and controls section of the ANDA (Volumes 1.1 - 1.2) and field copy certification (see Section XVII) has concurrently been sent to the New York District Office.

For your information, Endo Pharmaceuticals Inc. is an independent, stand-alone company formed from the recent business divestiture of Endo® Laboratories, L.L.C. (formerly a subsidiary of The DuPont Merck Pharmaceutical Company) from DuPont Merck.

This information is outlined in the Form FDA 3439 located in Section I. Dextroamphetamine Sulfate Tablets, USP, 5 mg will be manufactured at

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the application provision of 18 U.S.C. Section 331(j).

Any questions regarding this application may be directed to me at (516) 522-3306. Any written communications may be faxed to me at (516) 832-2291.

Sincerely,

Jeanne Stelter

Jeanne Stelter
Regulatory Associate

attachments
FDA-1997.doc

Endo

Endo Pharmaceuticals Inc.

April 23, 1998

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA 40-299; Dextroamphetamine Sulfate Tablets, USP, 5 mg
Amendment

Dear Mr. Sporn:

Reference is made to the original application for the subject product dated February 27, 1998 and accepted for filing March 2, 1998.

We are amending the application with an improved . . . Chromatographic Purity Method for Dextroamphetamine Sulfate USP drug substance.

The vendor-supplied Chromatographic Purity method for the drug substance submitted in the original application provides for the detection of two process impurities, and provides resolution of only those unknown impurities which lie in the region of these two knowns.

We have developed and validated an improved method, based on our finished product impurity method, which will resolve degradation products (unknowns) which previously appeared in the region of the Dextroamphetamine and solvent peaks, in addition to detecting the two process impurities.

The "new" method submitted herein supercedes the method included in the monograph for Dextroamphetamine Sulfate USP drug substance (Doc. No. MON9708827, Edition 2) submitted in the original application. The revised monograph (Doc. No. MON9708827, Edition 3) is enclosed.

500 ENDO BOULEVARD GARDEN CITY, N.Y. 11530 FAX (516) 832-2291

In addition to this improved test method, we are also submitting other information in order to clarify certain sections of the ANDA in order to facilitate your review.

All of the revisions are outlined in the attached table and tabbed according to the applicable section from the original application.

It is our expectation that the subject amendment will be considered in conjunction with the review of our original ANDA.

Please note that a "true" copy of this amendment has been forwarded to Ms. Brenda Holman at the New York District Office.

If you have any questions regarding this amendment, please contact me at (516) 522-3306.

Sincerely,

Jeanne Stelter

Jeanne Stelter
Regulatory Associate

attachments