

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-361

APPROVAL LETTER

JAN 31 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated February 18, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendment dated December 15, 2000.

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 and 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dextrostat® Tablets, 5 mg and 10 mg, respectively, of Shire Richwood Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

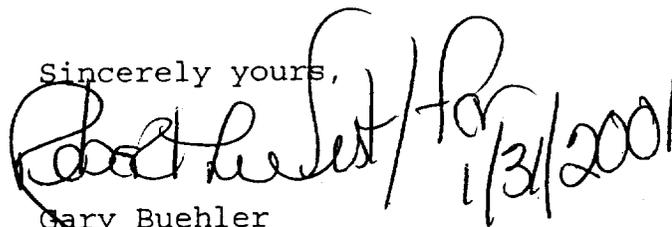
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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 that 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,

A handwritten signature in black ink, appearing to read "Gary Buehler", with a date "1/31/2001" written to the right of the signature.

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-361

APPROVED DRAFT LABELING

40-361
1/31/01
Labeling

Each tablet contains:
Dextroamphetamine sulfate, 10 mg
Usual Dosage:
See package brochure.
Dispense in a light, light-resistant container as defined in the USP.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Store at controlled room temperature 15°-30°C (59°-86°F).
BARR LABORATORIES, INC.
Pomona, NY 10970

R6-98
1120953020101



BARR LABORATORIES, INC.

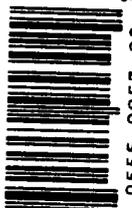


Dextroamphetamine Sulfate Tablets, USP
10 mg

Rx only

100 Tablets

NDC 0555-0953-02



23

0555-0953-02

Exp. Date: **AN 3/1/2001**
Lot No.: **SAMPLE**

Each tablet contains:
Dextroamphetamine sulfate, 5 mg
Usual Dosage:
See package brochure.
Dispense in a light, light-resistant container as defined in the USP.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Store at controlled room temperature 15°-30°C (59°-86°F).
BARR LABORATORIES, INC.
Pomona, NY 10970

R6-98
1120952020101



BARR LABORATORIES, INC.



Dextroamphetamine Sulfate Tablets, USP
5 mg

Rx only

100 Tablets

NDC 0555-0952-02



23

0555-0952-02

Exp. Date: **AN 3/1/2001**
Lot No.: **SAMPLE**

SAMPLE



**DEXTROAMPHETAMINE
SULFATE
TABLETS, USP** (U)



Revised MARCH 2000
1009520101

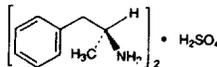
Rx only

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 *d*-alpha-methylphenethylamine, and is present in all forms of dextroamphetamine sulfate as the neutral sulfate. The structural formula is as follows:



(C₉H₁₃N), ·H₂SO₄

Molecular Weight: 368.49

Inactive ingredients:

Calcium sulfate, colloidal silicon dioxide, compressible sugar, magnesium stearate, microcrystalline cellulose, and starch.

The 5 mg also contains D&C yellow no. 10 aluminum lake and FD&C red no. 40 aluminum lake.

The 10 mg also contains FD&C red no. 40 aluminum lake and FD&C yellow no. 8 aluminum lake.

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 is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents.

CLINICAL PHARMACOLOGY:

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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 for:

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 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.

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

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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.

Methamphetamine Therapy: Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine 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 have not been performed.

Pregnancy: Teratogenic Effects:

Pregnancy Category C: Amphet-

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.

Methamphetamine Therapy: Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine 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 overdose, 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 have not been performed.

Pregnancy: Teratogenic Effects:

Pregnancy Category C: Amphetamine has 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. Amphetamines 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.

(Over)

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 pediatric patients, 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 pediatric patients 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 pediatric patient. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the pediatric patient'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 LD₅₀ 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.

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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 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 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 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

6

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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.

HOW SUPPLIED:

Dextroamphetamine Sulfate Tablets, USP are available as:

- 5 mg: Peach, round, flat-faced, beveled-edge, scored tablet. Debossed with 952/5 on the scored side and b on the other side. Available in bottles of:
100 NDC 0555-0952-02
- 10 mg: Pink, round, flat-faced, beveled-edge, scored tablet. Debossed with 953/10 on the scored side and b on the other side. Available in bottles of:
100 NDC 0555-0953-02

Dispense in a tight, light-resistant container as defined in the USP.

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

DEA Order Form Required.

**MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970**

Revised MARCH 2000
BR-952, 953

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-361

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4
2. ANDA # 40-361
3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
Pomona, NY 10970-0519

4. BASIS OF SUBMISSION
Reference Listed drug product: Dextrostat^R
Tablets by Shire Richwood approved in NDA #84-051.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug. There is no marketing exclusivity for this drug.

5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
NA
7. NONPROPRIETARY NAME
Dextroamphetamine Sulfate Tablets, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Original submission: 2-18-99
Acknowledgement: 3-16-99
Major amendment: 7-29-99
Amendment Response: 4-5-00
Major deficiency letter: 8-31-00
Reclassification to minor request: 9-7-00
Minor amendment response: 10-9-00
Minor deficiency letter: 11-22-00
Amendment Response: 12-15-00

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
For treatment of Narcolepsy Rx
and ADS

12. RELATED IND/NDA/DMF(s)

rug

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - All chemistry issues have been resolved.
Bioequivalence - Bioequivalence acceptable on 4/2/99 by M. Makary.
Labeling - Satisfactory dated 8/16/00.
EER - ~~Withheld~~ ok. 1/19/01 *ms*

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable, ~~pending satisfactory EER.~~ ^{OK}

*1/12/01
scg
1/24/01*

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

1-12-01

Page(s) 21

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chen Rev 4
9/12/01

NOV 22 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

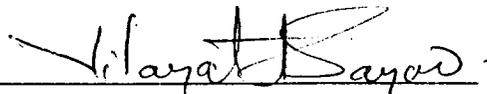
The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Please be aware that this application cannot be approved until deficiencies regarding DMF have been addressed satisfactorily by the DMF holder.
2. We acknowledge that you have lowered your impurity specification limits on release and stability for the drug product. We however believe that the limits you propose are still not justified by the data you have provided. You are requested to further lower these limits to be more in line with the actual data.

Sincerely yours,

ff



Florence Fang

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

AUG 31 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MAJOR deficiencies.

Deficiencies:

1. Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:
 - a. Although you are proposing _____ as an alternate supplier for Dextroamphetamine Sulfate, USP, and you have listed DMF _____ on your 356h form, you did not submit a Letter of Authorization to the Agency from _____ to review the DMF. You should be aware that the Agency does not have the authority to review this drug master file in the context of your ANDA without this letter. Please provide this information to the ANDA and be aware that at that time the DMF will be reviewed.
 - b. You have also stated that due to an unforeseen manufacturing site disaster, the current vendor _____ is no longer able to supply Barr with Dextroamphetamine Sulfate, USP raw material. If this statement is correct as written, you should withdraw _____ as a drug substance supplier.
2. Although, you have revised your Impurities testing specifications for the drug substance as requested, it is recommended that you lower your limits for knowns and unknowns be more in line with the actual data.
3. Although you have provided stability data for lots #309529001 and #309539001 manufactured using the _____ material, you did not provide the executed manufacturing and packaging records for these lots. This information should be submitted in support of the new drug substance supplier you are proposing. In addition, all batch reconciliation data, yields, deviation reports, in-process specs, etc. should be submitted to the application. We also request that you provide dissolution data on 12 tablets for review by the Division of Bioequivalence.

4. We note that you are withdrawing all previously proposed packaging configurations for both strengths of this product except the 100 fill bottle with screw cap. Please clarify if you are intending to market the bulk package.

5. Based on the release and stability data provided for the new lots of drug product manufactured using the Johnson Matthey material, it appears that the impurity levels proposed for release and stability are too high and should be lowered to be more in line with the actual data (known, unknown and total impurities).

Sincerely yours,

fs



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 29 1999

Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. You should include the designation in your Components and Composition statement for Calcium Sulfate.
2. It is unclear why the quantitative list of components for the 5 mg tablet lists 4 significant figures (5.000 mg) for the amount of Dextroamphetamine Sulfate, USP and for the 10 mg tablet a value of 10.00 (3 significant figures are reported).
3. Please clarify if you utilize USP Dextroamphetamine Sulfate material as a reference standard for the testing of the active raw material.
4. We recommend that you revise your testing specifications for the active drug substance to include testing for the 2 process impurities identified by the drug substance manufacturer
e). We note that you utilize this method in your finished product testing protocol.
5. Your raw materials testing for Magnesium Stearate, does not appear to meet current compendia. See USP 23. Supp. 10.
6. We note that the exhibit batches were manufactured over the course of several days. In accordance with 21 CFR, you are requested to clarify if you have established any time limits on production with regard to storage or holding of intermediates during each of the major steps of manufacture.
7. The exhibit batch sizes for both the 5 mg and 10 mg strengths were for tablets. The Master batch records you submitted were also for a batch size of ablets for each strength. Please clarify that your maximum proposed batch size for each strength is tablets.
8. You are requested to supply a complete list of **all** in-process testing with specifications that you intend to perform during the manufacture of all future batches of Dextroamphetamine Sulfate Tablets. Although you have included guidelines for tableting, in accordance with 21 CFR 211.110, valid in-process specifications for such characteristics shall be consistent with drug product final specifications.

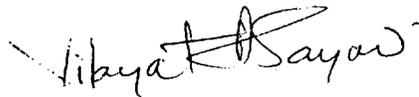
Examination and testing of samples shall assure that the drug product and in-process material conform to specifications. You are requested to establish and submit future in-process testing with reasonable specifications. Use of guidelines only is unacceptable.

9. You are also requested to commit to perform routine in-process blend homogeneity testing on future manufacturing batches of the drug product. It is recommended that the acceptance criteria for blend uniformity analysis be established at (mean value) with an RSD of . In addition you should outline the number of samples and what the sample size will be for this testing. It is recommended that the sample size of the blend should be greater than three times the weight of an individual dose.
10. Please clarify why the finished product COA for the 5 mg strength (lot #8R95204) does not appear to be included with any testing results. Refer to page 15-00048. A COA for the 10 mg strength (lot #8R95305) is included on page 15-00051 with full testing results. Testing results for lot # 8R95204 should be submitted to the Agency.
11. It is noted that the release specifications for the tablets include a specification for Water as, (where indicated). Please clarify if you intend to perform routine testing for Water on release and during stability for the tablets.
12. You are also requested to comment if you have detected any other impurities other than the 2 identifiable process impurities. We recommend that you include a specification for Single Unknown and Total Impurities (Known and Unknown).
13. Although you have included a testing summary of stability data for exhibit lots (#8R95204 and #8R95305), you should submit the authentic stability report forms with the actual testing dates.

B. In addition to the deficiencies listed above, please note and acknowledge the following:

You are requested to provide a list of excipient functionalities for each of the inactives used in the tablet formulation.

Sincerely yours,



for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40-361

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-361

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, 5 mg and 10 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,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-361

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, 5 mg and 10 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,



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

Dextroamphetamine Sulfate
5 mg and 10 mg Tablets
ANDA #40-361
Reviewer: Moheb H. Makary
File name: 40361DW.299

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
February 18, 1999

Review of Dissolution Data and Waiver Requests

The firm has submitted waiver requests for its dextroamphetamine sulfate, 5 mg and 10 mg tablets. To support the requests, the firm has submitted comparative dissolution profiles on its products and reference listed drug, Dextrostat[®] 5 mg and 10 mg tablets (Shire Richwood Inc.).

Dextrostat[®] is indicated in narcolepsy and in attention deficit disorder with hyperactivity.

Dextroamphetamine Sulfate is coded as an AA drug in the therapeutic equivalence evaluation book.

Formulations:

The formulations of Dextroamphetamine Sulfate Tablets, 5 mg and 10 mg are shown in Table I.

Dissolution Testing: (USP method)

Apparatus: 1 (basket)
Speed: 100 rpm
Medium: Deaerated Water
Volume: 500 mL
Sampling times: 15, 30, 45 and 60 minutes
Number of Tablets: 12
Test product: Barr's Dextroamphetamine Sulfate Tablets
5 mg, lot #8R95204
10 mg, lot #8R95305
Reference product: Shire Richwood's Dextrostat^R Tablets
5 mg, lot #B4462
10 mg, lot #B4322
Specification: in 45 minutes

Dissolution testing results are shown in Table II.

Comments:

1. Dissolution results for Barr Laboratories, Inc., test products Dextroamphetamine Sulfate Tablets, 5 mg and 10 mg are acceptable as summarized in Table II.
2. Waivers of bioequivalence study requirements for the test products may be granted based on CFR 320.22 (c).

Recommendations:

1. The dissolution testing conducted by Barr Laboratories, Inc., on its dextroamphetamine sulfate, 5 mg and 10 mg tablets, lots #8R95204 and #8R95305, respectively, is acceptable. Waivers of *in vivo* of bioequivalence study requirements for the test products are granted based on CFR 320.22 (c). From the bioequivalence point of view, the Division of Bioequivalence deems Barr's dextroamphetamine sulfate, 5 mg and 10 mg tablets to be bioequivalent to Dextrostat^R 5 mg and 10 mg tablets, respectively, manufactured by Shire Richwood Inc.
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 45 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

BWD 4/2/99

Barbara M. Davis

Date: 4/2/99

Concur:

Dale P. Conner
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 4/2/99

Table II. In Vitro Dissolution Testing

Drug (Generic Name): Dextroamphetamine Sulfate Tablet
 Dose Strength: 5 mg and 10 mg
 ANDA No.: 40-361
 Firm: Barr Laboratories, Inc.
 Submission Date: February 18, 1999
 File Name: 40361DW.299

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: x Paddle: RPM: 100
 No. Units Tested: 12
 Medium: Water Volume: 500 mL
 Specifications: in 45 minutes
 Reference Drug: Dextrostat[®] Tablet (Shire Richwood Inc.)
 Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #8R95204 Strength(mg) 5			Reference Product Lot #B4462 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	62		3.4	60		3.6
30	96		1.5	82		2.7
45	102		2.3	95		3.2
60	103		1.8	103		1.9

Sampling Times (Minutes)	Test Product Lot #8R95305 Strength(mg) 10			Reference Product Lot #B4322 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
15	50		4.5	54		2.6
30	84		3.8	84		3.0
45	98		2.4	102		1.1
60	101		2.3	102		0.9

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-361

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-361

DRUG PRODUCT: Dextroamphetamine
Sulfate, USP Tablets

FIRM: Barr Laboratories Inc.

DOSAGE FORM: Tablets

STRENGTH: 20 mg

CGMP STATEMENT/EIR UPDATE STATUS:

EER: ~~Pending~~ *Acceptable dated 1/19/01* ⁽⁶¹⁾

BIO INFORMATION:

The Division of Bioequivalence has found the application to be acceptable. The review was completed on 4/2/99 by M.Makary.

VALIDATION-DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
USP product, methods validation not required.

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

The firm includes a listing of the future testing specifications
for the drug product on stability. These are listed below: (See
next page)

Test	Limit
------	-------

Description

Dissolution

in, meets USP

Assay

*Impurities/Degradation Products

Water

*Revised upon request

The firm included a summary of 3 months of accelerated data at 40°C/75% RH for lots #8R95204 (5 mg) and #8R95305 (10 mg). Data for both container configurations (100 and 500 fill) were included for the 5 mg strength, and (100 and 1000 fill) for the 10 mg strength. The 500 fill for the 10 mg strength was bracketed. The firm did not submit any room temperature data, but they will test future room temperature stability at 25-30°C, ambient humidity. The firm proposes an 24 month expiration dating period.

Also included is a future stability commitment in accordance with FDA Guidelines.

**The 4/5/00 amendment included stability data (lots 309529001 and 309539001) for the lots manufactured using the / drug substance material). 3 months of accelerated data and 3 months of room temperature was submitted. The tablets were packaged in 100 count bottles with metal caps. Data was also provided for the bulk sample. The firm has stated that they do not propose to market the product in anything but a 100 count bottle at this time.

LABELING

The labeling review is acceptable as of 8/16/00.

STERILIZATION VALIDATION

NA

SIZE OF DEMONSTRATION BATCH

A description of the manufacturing and processing instructions is included beginning on page 11-00001. The process is a operation and begins with the

Page(s) 1

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releasable.

11/19/01

**In the 4/5/00 amendment, the firm is seeking approval of the alternate drug substance supplier . In support of this, the firm manufactured two batches (5 and 10 mg) using the material. Although the firm submitted stability data and finished product COAs for the new lots (#309529001 and 309539001).

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

Same

RECOMMENDATION: Approve

SIGNATURE:

DATE: January 16, 2001

Endorsements:

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-361

CORRESPONDENCE

Page(s) 1

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12/15/00

Barr Laboratories, Inc.

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 3 of 3

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

- **Current Revised Blank Stability Test Specifications and Test Record.**
- **Current Revised Finished Product Test Method TM-437K.**
- **Current Interim Stability Report.**

Identical copies of this Minor Amendment have been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Minor Amendment and response to the Agency's letter dated November 22, 2000. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur

Vice President, Quality and Regulatory Counsel

CM/jg

Enclosure

cc: New Jersey District Field Office

Baltimore District Field Office

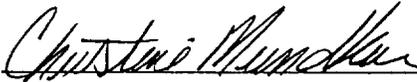
This submission is comprised of **Pages 1 through 100.**



Barr Laboratories, Inc.

Document Certification

Barr Laboratories, Inc. hereby certifies that a field copy of this Minor Amendment for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg is being submitted to the New Jersey and Baltimore district offices of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency, in accordance with 21 CFR § 314.71(b)



**Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.**

12-15-00

Date

noted jws
10/13/00

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

MA DRUG AMENDMENT

October 9, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

pm



MINOR AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10
MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your Minor Amendment Deficiency Letter for Chemistry, Manufacturing and Controls, dated August 31, 2000, and the September 11, 2000 phone conversation between Ms. Cassandra Sherrod, Project Manager, Team 7, Division of Chemistry II, OGD, FDA, and Joseph Greer of Barr Laboratories, Inc. regarding the reclassification of the August 31, 2000 Letter from a Major Amendment to Minor Amendment.

The following is stated in the August 31, 2000 letter:

DEFICIENCIES:

COMMENT 1

Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:

a.

Page(s) 4

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10/9/00

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 6 of 6

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

NMT
NMT
NMT
NMT
NMT

Please see pages 78 through 148 for the following:

- **Current Revised Blank Finished Product Test Specifications and Test Record.**
- **Current Revised Blank Stability Test Specifications and Test Record.**
- **Current Revised Finished Product Test Method TM-437I.**
- **Current Interim Stability Report.**

Identical copies of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Minor Amendment and response to the Agency's letter dated August 31, 2000. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory Counsel

CM/jg

Enclosure

cc: New Jersey District Field Office
Baltimore District Field Office

This submission is comprised of **Pages 1 through 148.**

Barr Laboratories, Inc.

September 7, 2000

Gary Buehler, Deputy Director, HFD-601
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

NC

REFERENCE: **CORRESPONDENCE**
ANDA 40-361
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to Barr's April 5, 2000 response to Major Amendment Letter dated July 29, 1999 and to Major Amendment Letter dated August 31, 2000 for Chemistry, Manufacturing and Controls in which the following is stated:

"The deficiencies presented below represent MAJOR deficiencies."

Barr respectfully requests that you reconsider the classification of the August 31, 2000 deficiency letter. This request is not typical of Barr Laboratories, Inc.; however, based upon the nature of the deficiencies noted, Barr believes that the classification of this deficiency letter as a "Major Amendment" is incorrect and unsubstantiated.

The deficiency letter is comprised of five deficiencies for the CMC portion. Of the five comments, three were addressed in our response letter dated April 5, 2000 and the remaining two only require Barr take action by tightening impurities/degradation specifications.

The following is stated in the August 31, 2000 letter:

DEFICIENCIES:

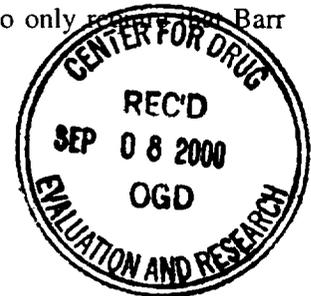
COMMENT 1

Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:

a.

1

For information to the FDA and to ensure that reviewed.



71
9-12-00

Page (s) 2

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9/7/00

Barr Laboratories, Inc.

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**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 4 of 4

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

Based upon the minor nature of the CMC comments and the fact that the information for Comment Numbers 1, 3 and 4 were already provided in Barr's response to Major Amendment Letter dated April 5, 2000, Barr respectfully requests the Agency to reclassify the August 31, 2000 CMC comment letter as a Minor Amendment.

If you have any questions about the forgoing or Barr's responses, please do not hesitate to call me at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur

Vice President, Quality and Regulatory Counsel

cc: Kassandra Sherrod, Project Manager, Div. of Chemistry II, Team 7 by Fax (301) 443-3839.

This correspondence is comprised of **Pages 1 through 4.**



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 5, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
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Rockville, Maryland 20855-2773

FPL
MAJOR AMENDMENT
AC

MAJOR AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your Major Amendment Letter for Chemistry, Manufacturing and Controls dated July 29, 1999 and the Labeling Comments dated September 29, 1999 in which the following is stated:

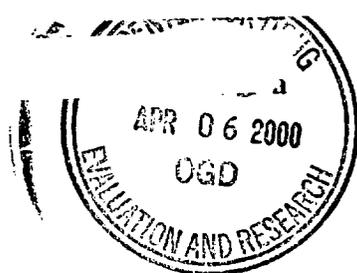
A. DEFICIENCIES:

COMMENT 1

You should include the in your Components and Composition statement for Calcium Sulfate.

RESPONSE 1

Calcium Sulfate, USP, is a combination of 70% Calcium Sulfate and



Page(s) 10

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releasable.

4/5/00

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**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 12 of 15

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

**mg and
ncluded**

B. In addition to the deficiencies listed above, please note and acknowledge the following:

the

RESPONSE TO B

LABELING COMMENTS:

INSERT

a. **DESCRIPTION**

- i. Revise the molecular weight to read, "Molecular Weight: 368.49"
- ii. Include "compressible sugar" as one of the inactive ingredients.

b. **INDICATIONS AND USAGE**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

OFFICE OF GENERIC DRUGS FOOD AND DRUG ADMINISTRATION

Page 13 of 15

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

Replace “children” with “pediatric patients (ages 3 to 16 years)”

c. PRECAUTIONS

Pediatric Use

Replace “children” with “pediatric patients” in the second paragraph.

d. OVERDOSAGE

Treatment

Replace the first paragraph with the following:

“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 overdose, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.”

e. DOSAGE AND ADMINISTRATION

Replace “children” with “pediatric patients” in the fourth, fifth and sixth paragraphs.

RESPONSE

Barr acknowledges the Agency’s request for revising labeling for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. The revised, final printed labeling are provided in Attachment

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 15 of 15

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

Please note that with the exception of the new raw material vendor, no changes have been made to the manufacturing procedures for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. See Attachment B and D updated sections for manufacturing and packaging procedures. Barr has updated the manufacturing masters for both strengths to incorporate guidelines/specifications for tablet hardness, weight, thickness and friability.

In the original ANDA dated February 18, 1999, Barr originally submitted for the package size of 100 and 500 tablets for the 5 mg strength, and package size of 100, 500 and 1000 tablets for the 10 mg strength of Dextroamphetamine Sulfate Tablets, USP. The recently manufactured lots using s drug substance that are being submitted for approval were packaged in 30 and 100 tablets for both strengths. Please note that at the present time, Barr does not seek to market the 5 mg strength in the bottle size of 30 or 500 tablets, nor the 10 mg strength in the bottle size of 30, 500 and 1000 tablets. The proposed package size for commercial marketing for both strengths is 100 tablets.

An identical copy of this Major Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Major Amendment and response to the Agency's letters dated July 29, 1999 and September 29, 1999. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory Counsel

0765.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 5, 2000

NEW CORRESP

NC/B10

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCE AMENDMENT

REFERENCE:

ANDA 40-361
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

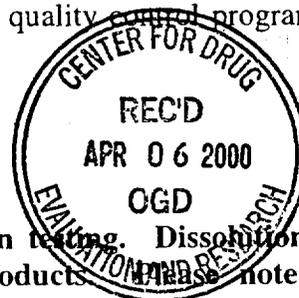
Reference is also made to your letter for Bioequivalence dated July 29, 1999 in which the following is stated:

COMMENT

Dissolution testing will need to be incorporated into the stability and quality control programs as specified in USP 23.

RESPONSE

Barr acknowledges the Agency's statement regarding Dissolution testing. Dissolution is a routine analysis performed on both stability and finished products. Please note that



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

Page 2 of 2

**REFERENCE: ANDA 40-361
 DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG
 AND 10 MG**

Dissolution testing is in the test method for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. A copy of method TM-437C was included in the original submission.

Please note that method TM-437C has since been updated to TM-437H. This method still includes dissolution testing in accordance with the current USP. As an attachment to this response please find a copy of the finished product test method TM-437H.

This completes the present Bioequivalence Amendment and response to the Agency's letter dated July 29, 1999. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur
Vice President, Quality and Regulatory Counsel

CM/ag
Enclosure
This submission is comprised of **Pages 1 through 00046.**

Barr Laboratories, Inc.

*ack for filing
S. Middleton
3/1/99*

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

February 18, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under section 505(j) of the Federal Food and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg**:

Barr would like the agency to note that the submission batches for each of these strengths of Dextroamphetamine Sulfate Tablets, USP were manufactured with active raw material supplied by [redacted]). Since the time of purchase and use of this drug substance in the referenced batches, the [redacted] was a victim of a facility disaster, i.e., an explosion. The manufacturing facility no longer exists. Please see Section VIII 2. of this application for a brief summary of the date and affected location. Although the manufacturing site is no longer functional, Barr acquired a DMF authorization letter from [redacted] for the active raw material that was used by Barr to manufacture the submission batches. In addition, after the approval of this application, Barr intends to use its remaining inventory of the [redacted] material to manufacture future finished product batches until such time that we are able to locate and qualify an alternate source of active.

This application is provided in duplicate, both as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 3 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in an orange binder. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER.

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GENERIC DRUGS

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992 is a Debarment Certification Statement. In accordance with 21 CFR §314.94 (d) (5), a "Field Copy" of this application has been forwarded to the New Jersey District Office.

Your earliest acknowledgment to this application will be very much appreciated. If you have any questions, please contact me at (914) 353-8432.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur
Vice President, Quality and Regulatory
Counsel

CM/krq