CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 040436Orig1s000

Name: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

Sponsor: Mallinckrodt Inc.

Approval Date: January 29, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

APPROVAL LETTER

ANDA 40-436

JAN 29 2002

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your abbreviated new drug application dated May 31, 2001, 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 amendments dated November 16, December 6, and December 10, 2001; and January 14, 2002.

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,

Gary Buehler 1/29/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-436
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-645/R.Brown/ 1/22/02
HFD-645/B.Arnwine/1/15/02 1/23/02
HFD-617/K.Sherrod/1/11/02 1/22/02
HFD-613/K.Lee/ 1/23/02 No changes in PIO
HFD-613/C.Hoppes/ 1/23/02

v:/firmsam/mallinckrodt/ltrs&rev/40436d.apf
F/T by rad1/17/02

APPROVAL

conc satisfactory. 1/24/02
1/29/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

LABELING

DEXTROAMPHETAMINE SULFATE TABLETS, USP
5 mg and 10 mg
Rx only

C II

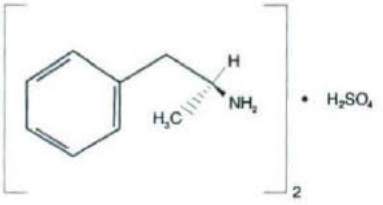
WARNING

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 *d*-alpha-methylphenethylamine, and is present in all forms of Dextroamphetamine Sulfate, Tablets, USP as the neutral sulfate. It has the chemical formula of $(C_9H_{13}N)_2 \cdot H_2SO_4$ and a molecular weight of 368.49.

Structural Formula:



$C_{18}H_{28}N_2O_4S$
368.49

Each tablet, for oral administration, contains dextroamphetamine sulfate USP, 5 mg or 10 mg. Each tablet also contains the following inactive ingredients: Microcrystalline Cellulose, Povidone, Silicon Dioxide, and Stearic Acid.

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 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 amphetamine.

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 effect 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, USP have not been performed.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Dextroamphetamine has been shown to have embyrotoxic 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 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 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 tablets 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 pediatric patients under 12 years of age; however, when it does, Dextroamphetamine Sulfate Tablets, USP 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 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 require continued therapy.

HOW SUPPLIED

Each Dextroamphetamine Sulfate Tablet, USP (5 mg) contains dextroamphetamine sulfate 5 mg. It is available as triangle shaped, white to off white tablet debossed with a number "5" and a bisect on one side and an "M" in a box on the other.

Bottles of 30 . . . . . NDC No. 0406-8958-03
Bottles of 100 . . . . . NDC No. 0406-8958-01
Bottles of 1000 . . . . . NDC No. 0406-8958-10
Unit Dose (4x25) . . . . . NDC No. 0406-8958-63

Each Dextroamphetamine Sulfate Tablet, USP (10 mg) contains dextroamphetamine sulfate 10 mg. It is available as diamond shaped, white to off white tablet debossed with a number "10" and a partial quadrisect on one side and an "M" in a box on the other.

Bottles of 30 . . . . . NDC No. 0406-8959-03
Bottles of 100 . . . . . NDC No. 0406-8959-01
Bottles of 1000 . . . . . NDC No. 0406-8959-10
Unit Dose (4x25) . . . . . NDC No. 0406-8959-63

Dispense in a tight container with a child-resistant closure as defined in the USP. Store at controlled room temperature 15° - 30°C (59° - 86°F) [see USP].

DEA Order Form Required.

tyco
Healthcare

Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.

Mallinckrodt

Rev 103101

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-436 Date of Submission: November 16 and December 10, 2001

Applicant's Name: Mallinckrodt

Established Name: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (30's, 100's, & 1000's) FPL submitted 11/16/01 are acceptable for approval.
- Carton Labels: (100's) FPL submitted 11/16/01 are acceptable for approval.
- Blister Labeling: (25's) FPL submitted 11/16/01 are acceptable for approval.
- Professional Package Insert Labeling: FPL sumbmitted 12/10/01 is acceptable for approval.
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition? NO
- What is the RLD on the 356(h) form: DextroStat
- NDA Number: 84-051
- NDA Drug Name: DextroStat
- NDA Firm: Shire Richwood
- Date of Approval of NDA Insert and supplement #: Nov. 3, 1999;NDA 17-078S-034
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by Side Side by Side
- Basis of Approval for the Carton Labeling: Based on container

FOR THE RECORD:

1. MODEL LABELING: Although the RLD is DextroStat Tablets by Shire USA, the model used was Dexedrine labeling approved November 3, 1999 (NDA 17-078/S-034). The Dexedrine labeling was used to approve the labeling of DextroStat Tablets.
2. INACTIVE INGREDIENTS: Consistent with application (see page 148 Vol. 1.1).
3. PATENTS/EXCLUSIVITIES: No unexpired patents or exclusivities.
4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well-closed containers
   - RLD: CRT
   - ANDA: CRT
5. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in well-closed containers
   - RLD: Dispense in a tight container as defined in the USP.
   - ANDA: Dispense in a tight container with a child resistant closure as defined in the USP
6. PACKAGE CONFIGURATION
   - RLD: Bottles of 100's
   - ANDA: 30's, 100's, 1000's and Unit-Dose Packs of 100's
7. CONTAINER/CLOSURE
   - Container: Bottles are HDPE
   - Closure: 5 mg bottles of 30's and 100's and 10 mg bottles of 30's are CRC. 5 mg bottles of 1000's and 10 mg bottles of 100's and 1000's are non-CRC. (b) (4)

8. FINISHED DOSAGE FORM

- RLD:
- ANDA: Consistent with application except the insert labeling should describe the tablets as white to off-white. The 5 mg tablet is bisected and the 10 mg is "quadrisected" as is the RLD.

Date of Review: December 12, 2001 Date of Submission: 11/16/01 and 12/10/01

Primary Reviewer: Koung Lee Date: 12/21/01

Team Leader: Charlie Hoppes Date: 12/21/01

cc: ANDA: 40-436
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40436.AP.LABELING
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-436 Date of Submission: May 31, 2001

Applicant's Name: Mallinckrodt

Established Name: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

Labeling Deficiencies:

1. CONTAINERS (30's, 100's, and 1000's)

   Revise the "Each tablet contains" statement to reflect the correct strength for the 10 mg bottles.

2. UNIT DOSE BLISTER (25's)

   We encourage you to differentiate the two different strengths from each other by using contrasting colors and/or boxing, or any other means.

3. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight to read 368.49 per USP 24.

      ii. Revise "H2SO4" to read as "H_2S0_4".

   b. CLINICAL PHARMACOLOGY

      Revise the second paragraph to read "...mental and behavioral effects in children, nor..."

   c. PRECAUTIONS (Drug Interactions)

      Replace [redacted] (b) (4) therapy" with "Methenamine therapy" and delete "the" in "...the efficacy is".

   d. OVERDOSAGE

      i. Replace "LD50" with "LD_{50}" in the third sentence of the first paragraph.

      ii. Replace [redacted] (b) (4) with "phentolamine" in the second to the last sentence of the last paragraph.

      iii. Add the following as the last paragraph.

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

   e. HOW SUPPLIED

      i. Revise the description of both the 5 mg and 10 mg tablet to read "...white to off white tablet debossed with a number "5"..." and "...white to off white tablet debossed with a number "10"...", respectively.

      ii. Add "(see USP)" to the storage temperature statement.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. MODEL LABELING: Although the RLD is DextroStat Tablets by Shire USA, the model used was Dexedrine labeling approved November 3, 1999 (NDA 17-078/S-034). The Dexedrine labeling was used to approve the labeling of DextroStat Tablets.
2. INACTIVE INGREDIENTS: Consistent with application (see page 148 Vol. 1.1).
3. PATENTS/EXCLUSIVITIES: No unexpired patents or exclusivities.
4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well-closed containers
   - RLD: CRT
   - ANDA: CRT
5. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in well-closed containers
   - RLD: Dispense in a tight container as defined in the USP.
   - ANDA: Dispense in a tight container with a child resistant closure as defined in the USP
6. PACKAGE CONFIGURATION
   - RLD: Bottles of 100's
   - ANDA: 30's, 100's, 1000's and Unit-Dose Packs of 100's
7. CONTAINER/CLOSURE
   - Container: Bottles are HDPE
   - Closure: 5 mg bottles of 30's and 100's and 10 mg bottles of 30's are CRC. 5 mg bottles of 1000's and 10 mg bottles of 100's and 1000's are non-CRC. (b) (4)
8. FINISHED DOSAGE FORM
   - RLD:

   - ANDA: Consistent with application except the insert labeling should describe the tablets as white to off-white. The 5 mg tablet is bisected and the 10 mg is "quadrisected" as is the RLD.

Date of Review: Juyly 18, 2001 Date of Submission: May 31, 2001

Primary Reviewer: Koung Lee Date: 8/17/01

Team Leader: Charlie Hoppes Date: 8/17/01

cc: ANDA: 40-436
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40436.NA.LABELING Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 2

2. ANDA # **40-436**

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: DEXTROSTAT® Tablets
Innovator Company: Shire Richwood (NDA #84-051)
Patent Certification and Exclusivity Statement are provided (pp. 009-017)

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
DEXTROSTAT®

7. NONPROPRIETARY NAME
Dextroamphetamine Sulfate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: Original ANDA

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Orig. submission	7/2/01	Acknowledgement letter	7/2/01
		Bio review	7/26/01
		Labeling review	8/17/01
		Deficiency letter	10/30/01
Amendment	11/16/01	Labeling review	12/21/01
Amendment (telephone)	12/6/01		
Amendment (telephone)	1/14/02		

This review covers submission dated 11/16, 12/6/01 and 1/14/02.

10. (PROPOSED) INDICATION(S) FOR USE
For use in Narcolesy and Attention Deficit Disorder with Hyperactivity

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF #15385 (b) (4)
Other DMFs are identified in the container/closure section.

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

(+)-α-Methylphenethylamine sulfate

Molecular weight: 368.49 Formula: $(C_9H_{13}N)2.H_2SO_4$

16. RECORDS AND REPORTS None -

17. COMMENTS
a) Application is adequate for approval.
b) Labeling: Acceptable dated 12/21/01
c) Bio: Waiver granted dated 7/18/01
d) DMF #15385: Adequate dated 12/18/01
e) Methods validation is not required, both items are compendial.
f) Establishment evaluation report found acceptable 7/9/01.

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVED

19. REVIEWER: Raymond Brown

DATE COMPLETED: January 15, 2002

20. COMPONENT AND COMPOSITION **Adequate -**

Ingredient	Per 5 mg Tablet	Per 10 mg Tablet	Per ANDA Batch[3]	Role in Formulation
Dextroamphetamine Sulfate USP	5.000 mg	10.000 mg	(b) (4)	Active ingredient
Microcrystalline Cellulose NF (b) (4)				(b) (4)
Povidone USP (b) (4)				
(b) (4)				
Silicon Dioxide NF (b) (4)				
Stearic Acid NF				
Total	125.00 mg	250.00 mg	(b) (4)	

(b) (4)

Following this page, 9 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

Expiration dating period:
24 months requested

30. CONTROL NUMBERS
Handled by field investigator

31. SAMPLES AND RESULTS **N/A** -
Drug substance and drug product are compendia.

32. LABELING - **Acceptable** -
See review dated 12/21/01.

33. ESTABLISHMENT INSPECTION **Acceptable –**
See report dated 7/9/01.

34. BIOEQUIVALENCY STATUS **Acceptable –**
See Review of a Waiver Request, dated 7/18/01.

35. ENVIRONMENTAL IMPACT CONSIDEREDS/CATEGORICAL EXCLUSION **Adequate –**
Applicant has file claim of categorical exclusion from the requirement for an environmental assessment for Dextroamphetamine Sulfate Tablets USP.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.

Yes ✓ - No _____ -

If no, explain reasons(s) below:

SPOT Yes _____ - No ✓ -

37. DMF Checklist for ANDA # 40-436 REVIEW # 2

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
15385	II/Dextroamphetamine Sulfate/ Mallinckrodt	1	Adequate	12/18/01

Comments:

(b) (4)	4
	4
	4
	4
	4
	4

Comments:

ACTION CODES:

(1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").;

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]		(b) (4) 4		
		4		
		4		
		4		
		4		
		4		
		4		

Comments:

ACTION CODES:

(8) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(9) Type 1 DMF;
(10) Reviewed previously and no revision since last review;
(11) Sufficient information in application;
(12) Authority to reference not granted;
(13) DMF not available;
(14) Other (explain under "Comments").;

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	(b) (4)	4		
		4		

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES:
(15) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(16) Type 1 DMF;
(17) Reviewed previously and no revision since last review;
(18) Sufficient information in application;
(19) Authority to reference not granted;
(20) DMF not available;
(21) Other (explain under "Comments").;

cc: ANDA 40-436
Division File
FIELD COPY

Endorsements
HFD-645/RBrown/1/15/02
HFD-645/BTArnwine/1/15/02

F/T by cll/1/17/02

V:\firmsam\Mallinckrodt\ltrs&rev\40436r2.afr.doc

CHEMISTRY REVIEW - APPROVED

1. CHEMISTRY REVIEW NO. 1

2. ANDA # **40-436**

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: DEXTROSTAT® Tablets
Innovator Company: Shire Richwood (NDA #84-051)
Patent Certification and Exclusivity Statement are provided (pp. 009-017)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
DEXTROSTAT®

7. NONPROPRIETARY NAME
Dextroamphetamine Sulfate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: Original ANDA

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Orig. submission	~~7/2/01~~ 5/31/01	Acknowledgement letter	7/2/01
		Bio review	7/18/01
		Labeling review	Pending

This review covers submissions dated 7/2/01.

10. (PROPOSED) INDICATION(S) FOR USE
For use in Narcolesy and Attention Deficit Disorder with Hyperactivity

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF #15385 (b) (4)
Other DMFs are identified in the container/closure section.

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

(b) (4)

(+)-α-Methylphenethylamine sulfate

Molecular weight: 368.49 Formula: $(C_9H_{13}N)2.H_2SO_4$

16. RECORDS AND REPORTS None -

17. COMMENTS
a) Application contains MINOR CMC deficiencies
b) Labeling: Pending
c) Bio: Waiver granted dated 7/18/01
d) DMF #15385: inadequate dated 9/27/01
e) Methods validation is not required, both items are compendia.
f) Establishment evaluation report pending.

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVABLE

19. REVIEWER: Raymond Brown

DATE COMPLETED: September 27, 2001

20. COMPONENT AND COMPOSITION **Adequate -**

Ingredient	Per 5 mg Tablet	Per 10 mg Tablet	Per ANDA Batch[3]	Role in Formulation
Dextroamphetamine Sulfate USP	5.000 mg	10.000 mg	(b) (4)	Active ingredient
Microcrystalline Cellulose NF (b) (4)				(b) (4)
Povidone USP (b) (4)				
Silicon Dioxide NF (b) (4) (b) (4)				
Stearic Acid NF				
Total	125.00 mg	250.00 mg	(b) (4)	

(b) (4)

Following this page, 8 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

Expiration dating period:
24 months requested

30. CONTROL NUMBERS
Handled by field investigator

31. SAMPLES AND RESULTS **N/A -**
Drug substance and drug product are compendia.

32. LABELING - **Unacceptable -**
See review dated 7/18/01.

33. ESTABLISHMENT INSPECTION - **Acceptable –**
See report dated 7/9/01.

34. BIOEQUIVALENCY STATUS **Acceptable –**
See Review of a Waiver Request, dated 7/18/01.

35. ENVIRONMENTAL IMPACT CONSIDEREDS/CATEGORICAL EXCLUSION **Adequate –**
Applicant has file claim of categorical exclusion from the requirement for an environmental assessment for Dextroamphetamine Sulfate Tablets USP.

Applicant certifies that to the best of its knowledge and in its opinion, the manufacture of this product is in compliance with all federal, state and local environmental protection requirements. (p. 1680).

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.

Yes ✓ - No _____ -

If no, explain reasons(s) below:

SPOT Yes _____ - No ✓ -

37. DMF Checklist for ANDA # 40-436 REVIEW # 1

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
15385	II/Dextroamphetamine Sulfate/ Mallinckrodt	1	Inadequate	9/27/01

Comments:

(b) (4)

s	4
	4
	4
n	4
	4
	4

Comments:

ACTION CODES:

(1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(2) Type I DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").;

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted] (b) (4)		4		
		4		
		4		
		4		
		4		
		4		
		4		

Comments:

ACTION CODES:

(8) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(9) Type 1 DMF;
(10) Reviewed previously and no revision since last review;
(11) Sufficient information in application;
(12) Authority to reference not granted;
(13) DMF not available;
(14) Other (explain under "Comments").;

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted] (b) (4)		4		
		4		

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES:

(15) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
(16) Type 1 DMF;
(17) Reviewed previously and no revision since last review;
(18) Sufficient information in application;
(19) Authority to reference not granted;
(20) DMF not available;
(21) Other (explain under "Comments").;

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **40-436** APPLICANT: **Mallinckrodt Inc.**

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

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. [redacted] (b) (4)
2.
3.
4.
5.
6.
7.
8. Drug Master File #15385 is deficient and the DMF holder has been advised of the deficiencies.

Sincerely yours,

10/29/01

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

cc: ANDA 40-436
Division File
FIELD COPY
DUP ANDA

Endorsements
HFD-645/RBrown/9/27/01
HFD-645/BTArnwine/10/19/01
HFD-617/KSherrod/10/10/01

RBrown 10/24/01
BTArnwine 10/26/01
KSherrod 10/29/01

F/T by rad10/22/01
v:\firmsam\Mallinckrodt\ltrs&rev\40436R1.NAFf

CHEMISTRY REVIEW - Not APPROVABLE – Minor

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

BIOEQUIVALENCE REVIEWS

JUL 26 2001

Dextroamphetamine Sulfate Tablets, USP
5 mg and 10 mg
ANDA #40-436
Reviewer: James E. Chaney
V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40436DW.501

Mallinckrodt, Inc.
St. Louis, MO
Submission Date:
May 31, 2001

Review of Dissolution Data and Waiver Requests

I. Introduction

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 comparing its tablets with the reference listed drugs, Dextrostat® 5-mg and 10-mg tablets (Shire Richwood, Inc., ANDA 84-051).

Dextrostat® is indicated for narcolepsy and attention deficit disorder with hyperactivity.

Dextroamphetamine sulfate tablet is coded as an AA drug in the Orange Book.

II. Formulations

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

III. Dissolution Testing

Method	(USP method)
Apparatus:	1 (basket)
Speed:	100 rpm
Medium:	(b) (4) water
Volume:	500 mL
Sampling times:	15, 30, 45 and 60 minutes
Number of Tablets:	12
Test product:	Dextroamphetamine sulfate tablets 5-mg, lot #MHSC0097 10-mg, lot #MHSC0098
Reference product:	Shire Richwood's Dextrostat® tablets 5-mg, lot #B5562 10-mg, lot #B5572
Specification:	NLT 75% (Q) in 45 minutes

Dissolution testing results are shown in Table 2.

IV. Comments

1. Dissolution results for Mallinckrodt's 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 21 CFR 320.22 (c).

L

3. All inactive ingredients in the formulation were present at or below levels cited for oral tablets in the "Inactive Ingredient Guide" published by the Division of Drug Information and Resources in January 1996.

V. Recommendations

1. The dissolution testing conducted by Mallinckrodt, Inc. on its dextroamphetamine sulfate, 5-mg and 10-mg tablets, lots #MHSC0097 and #MHSC0097, respectively, is acceptable. Waivers of *in vivo* of bioequivalence study requirements for the test products are granted based on 21 CFR 320.22 (c). From the bioequivalence point of view, the Division of Bioequivalence deems Mallinckrodt's dextroamphetamine sulfate, 5-mg and 10-mg tablets to be bioequivalent to Dextrostat® 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 24 apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than 75% (Q) of the labeled amount of the drug product is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 7/18/2001

Concur: Dale P. Conner Date 7/26/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/071801
V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40436DW.501

Table 1. Formulation of Dextroamphetamine Sulfate Tablets, USP		
Ingredient	5-mg Tablet	10-mg Tablet
Dextroamphetamine Sulfate USP	5.000	10.000
Microcrystalline Cellulose NF, (b) (4)	(b) (4)	(b) (4)
(b) (4)		
Povidone USP (b) (4)		
(b) (4)		
Silicon Dioxide NF (b) (4)		
Stearic Acid NF		
Total	**125.00**	**250.00**
(b) (4)		

Table 2. **Results of *In Vitro* Dissolution Testing**						
Sampling Times (Minutes)	Test Product Lot # MHSC0097 Strength(mg) 5			Reference Product Lot # B5562 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.7	(b) (4)	2	75.3	(b) (4)	13
30	96.7		3	96.2		7
45	94.3		3	98.9		2
60	92.7		3	98.7		2
Sampling Times (Minutes)	Test Product Lot # MHSC0098 Strength(mg) 10			Reference Product Lot # B5572 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
15	97.4	(b) (4)	2	86.1	(b) (4)	8
30	94.7		2	96.9		2
45	92.5		2	97.1		2
60	91.0		2	94.2		2

BIOEQUIVALENCY COMMENTS

ANDA: 40-436 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, USP
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 24.

In future submissions you should include the address of the laboratory where the dissolution studies were conducted.

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

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

CC: ANDA 40-436
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 7/18/2001
HFD-652/ Y. Huang 7/18/2001
HFD-617/ K. Scardina 7/20/01
HFD-650/ D. Conner 7/26/01

FILENAME

BIOEQUIVALENCY - ACCEPTABLE

Submission date: May 31, 2001

1. DISSOLUTION WAIVER (DIW) OK

Strengths: 5-mg
Outcome: AC

2. DISSOLUTION WAIVER (DIW) OK

Strengths: 10-mg
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The dissolution data were found acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 40-436 SPONSOR : Mallinckrodt, Inc.
DRUG AND DOSAGE FORM: Dextroamphetamine Sulfate Tablets, USP
STRENGTH(S): 5-mg, 10-mg
TYPES OF STUDIES: Dissolution
CINICAL STUDY SITE: NA
ANALYTICAL SITES: NA
STUDY SUMMARY: Dissolution studies are acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic: No New facility: No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James E. Chaney BRANCH: I
INITIAL: JEC DATE: 7/18/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: [signature] DATE: 7/18/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : [signature] DATE : 7/26/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

OTHER REVIEWS

DIVISION REVIEW SUMMARY

ANDA 40-436 **DRUG PRODUCT:** Dextroamphetamine Sulfate

FIRM: Mallinckrodt Inc. **DOSAGE FORM:** Tablets

STRENGTH: 5 mg and 10 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable -
EER found ACCEPTABLE dated 7/9/01.

BIO INFORMATION: Adequate -
Bio waiver granted 7/18/01.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required, both items are compendia.

STABILITY: Adequate -

(b) (4)

An expiration dating of 24 month has been granted.

LABELING: Acceptable -
See Review of Professional Labeling dated 12/21/01.

STERILIZATION VALIDATION: N/A -

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Batch no. B05260 (Mallinckrodt, Inc.) used. DMF 15385 found **ADEQUATE** dated 12/18/01.

SIZE OF STABILITY BATCHES - Adequate -

(b) (4)

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

The proposed maximum production batch sizes are [redacted] (b) (4) tablets (5 mg) and [redacted] (b) (4) tablets (10 mg). The manufacturing process is [redacted] (b) (4)

RECOMMENDATION:

APPROVED

cc: 40-436

Endorsements:

HFD-645/RBrown/1/9/02
HFD-645/BArnwine/1/1/15/02

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F/T by rad1/17/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040436Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-436 Applicant Mallinckrodt Inc.
Drug Dextroamphetamine Sulfate Strength 5mg and 10mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
1. Project Manager KSherod	Date 1/9/02	Date 1/23/02
Review Support Br	Initials [illegible]	Initials

Application Summary:

Original Rec'd date 6/5/01
Date Acceptable for Filing 6/5/01
Patent Certification (type) II
Date Patent/Exclus.expires —
Citizens Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
(If YES, check PETS)
Pediatric Exclusivity (Tracking PETS)
Date checked 1/11/02 NDA# 84-051
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 7/9/01
Date of Office Bio Review 7/26/01
Date of Labeling Approv. Sum 12/2/01
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
30 Day Clock Start ____ End ____
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date ____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date ____
Comments:

2. Div. Dir./Deputy Dir.	Date 1/23/02	Date 1/24/02
Chemistry Div. I or II	Initials [illegible]	Initials [illegible]
Comments: CMC satisfactory		
3. Frank Holcombe	Date ____	Date ____
Assoc. Dir. For Chemistry	Initials ____	Initials ____
Comments: (First generic drug review)		
4. Pat Beers Block	Date 1/24/02	Date ____
Supv., Review Support Branch	Initials [illegible]	Initials ____

EER Status: Acceptable for all facilities as of 7/9/01 (none OAI)

Bioequivalence sites:
Clinical site: N/A
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status: ____
Reason:

Analytical site: N/A
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status: ____
Reason:

Bioequivalence office level sign off: Waiver granted based on 21 CFR 320.22(c) Dissolution data was found acceptable 7/26/01
Labeling Status: Acceptable 12/21/01
Microbiology status: N/A
Patent Certification: Para IV, no exclusivity granted to RLD.
Controlled Correspondence/Cit.Pet: N/A
Comments: RLD = 17-078 (used for labeling review)
84-051 (used for ANDA submission)

REVIEWER:	DRAFT RECEIPT	FINAL ACTION

5. Greg Davis
Supv., Reg. Support Branch

Date 28-JAN-2002 Initials [illegible]

Date 28-JAN-2002 Initials [illegible]

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD-Zestoretic tablets 5mg-10mg ANDA 84-051 Shire Richwood Inc

Comments:
no patent or exclusivity issues exist - OK for full approval.

6. Peter Rickman
Acting Director, DLPS

Date 1/29/2002 Initials [illegible]

Date 1/29/02 Initials [illegible] for

Comments: Acceptable ES dated 7/3/01 (Verified 9/29/02). No O.N.I. labels noted. Bio waiver granted under 21 CFR 320.22(c). RLD is "AA" dated in Orange Book. Office-level bio endorsed 7/26/01. FPL acceptable 12/21/01. CMC acceptable 1/23/02. Methods validation is not required.

7. Robert L. West
Acting Deputy Director, OGD

Date 1/29/02 Initials [illegible]

Date 1/29/2002 Initials Robert L. West

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments: This application is recommended for approval. It is not impacted by the current CR sent by Shire on Adderall.

8. Gary Buehler
Director, OGD
Comments:

Date 1/29/02 Initials GB

Date 1/29/02 Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Kassandra Sherrod
Review Support Branch

Date 1/29/02 Initials [illegible]

Date 1/29/02 Initials [illegible]

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:00 Time notified of approval by phone 2:00 Time approval letter faxed

FDA Notification:
1/29 Date e-mail message sent to "OGD approvals" account
1/29 Date Approval letter copied to"//cder/drugapp" directory

v:\reports\approval\approvrou

MINOR AMENDMENT

ANDA 40-436

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 30 2001

TO: APPLICANT: Mallinckrodt Inc. TEL: 314-654-6258

ATTN: Marianne Robb FAX: 314-654-6496

FROM: Kassandra Sherrod PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry, labeling and bioequivalence

JS

OCT 30 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **40-436** APPLICANT: **Mallinckrodt Inc.**

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

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

(b) (4)

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. Drug Master File #15385 is deficient and the DMF holder has been advised of the deficiencies.

Sincerely yours,

for

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

BIOEQUIVALENCY COMMENTS

ANDA: 40-436 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets, USP
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 24.

In future submissions you should include the address of the laboratory where the dissolution studies were conducted.

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

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-436 Date of Submission: May 31, 2001

Applicant's Name: Mallinckrodt

Established Name: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

Labeling Deficiencies:

1. CONTAINERS (30's, 100's, and 1000's)

   Revise the "Each tablet contains" statement to reflect the correct strength for the 10 mg bottles.

2. UNIT DOSE BLISTER (25's)

   We encourage you to differentiate the two different strengths from each other by using contrasting colors and/or boxing, or any other means.

3. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight to read 368.49 per USP 24.

      ii. Revise "H2SO4" to read as "H_2S0_4".

   b. CLINICAL PHARMACOLOGY

      Revise the second paragraph to read "...mental and behavioral effects in children, nor..."

   c. PRECAUTIONS (Drug Interactions)

      Replace [redacted] (b) (4) therapy" with "Methenamine therapy" and delete "the" in "...the efficacy is".

   d. OVERDOSAGE

      i. Replace "LD50" with "LD_{50}" in the third sentence of the first paragraph.

      ii. Replace [redacted] (b) (4)" with "phentolamine" in the second to the last sentence of the last paragraph.

      iii. Add the following as the last paragraph.

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

   e. HOW SUPPLIED

      i. Revise the description of both the 5 mg and 10 mg tablet to read "...white to off white tablet debossed with a number "5"..." and "...white to off white tablet debossed with a number "10"...", respectively.

      ii. Add "(see USP)" to the storage temperature statement.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA# 40-436 FIRM NAME Mallinckrodt Inc

RELATED APPLICATION(S) N/A

DRUG NAME: Dextroamphetamine Sulfate

DOSAGE FORM: Tablets USP, 5 mg & 10 mg

FIRST GENERIC? N/A

Electronic Submission (Chem) CMC Labeling & E-mail notification sent gave to Richard

Team Leader Brenda Arnwine

Labeling Reviewer Kourg Lee KXL

Random Assignment RNT

Micro Reviewer N/A

Pharmacodynamic study (Dr. Fanning) N/A

Letter Date 5/31/2001 Received Date 6/5/2001

		YES	NO
	Comments EC2 ✓ On Cards ✓ Therapeutic Code 2020500 anorexigenic agents	✓	
	Methods Validation Package (3 copies) GLP (Required for Non-USP drugs)	✓	
	Archival, and Review copies ✓ Field copy certification (original signature)	✓	
	Cover Letter	✓	
	Table of Contents	✓	

Dextroamphetamine Sulfate Tablets USP
Pg. 529

Sec. I	Signed and Completed Application Form (356h) (Statement regarding Rx/OTC Status)	✓	
Sec. II	Basis for Submission RLD Dextrostat Firm Shire Richwood Is an ANDA suitability petition required?____ If yes, consult needed for pediatric study requirement.	✓	
Sec. III	Patent Certification 1. Paragraph? II 2. Expiration of Patent____ A. Pediatric Exclusivity Submitted?____ B. Pediatric Exclusivity Tracking System checked?____	✓	
	Exclusivity Statement ✓	✓	
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓	
Sec. V	Labeling 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓	✓	
Sec. VI	Bioavailability/Bioequivalence 1. Financial certification (Form FDA 3454) X and Disclosure statement (Form 3455)____ (for BE studies only!) 2. In Vivo Study Protocol(s) N/A 3. In Vivo Study(ies) N/A 4. Computer Disk Submitted____ 5. Request for Waiver of In Vivo Study(ies) ✓ 6. In Vitro Dissolution Data ✓ 7. Formulation Data Same? (Comparison of all Strengths) ✓ (Ophthalmics, Otics, Externals, Parenterals) 8. Paragraph IV bio study acceptable for filing N/A 9. Lot numbers of products used in Bio-study ✓ 10. DSI inspection request needed?____ 1st Generic____ 1st study for site____ Other____ E-mail notification to bio PMs sent____ RLD is "AA" rated	✓	

(b) (4)

Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓ Review notes.	✓	
Sec. VIII	**Raw Materials Controls** 1. Active Ingredients a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ____ c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ – Vol. 1.4 (Methods Section) g. CFN numbers ____ 2. Inactive Ingredients a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' certificates of analysis (specifications and test results) ✓ d. Applicant certificate of analysis ✓	✓	✓
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing ✓ 2. CGMP Certification ✓ 3. CFN numbers ____	✓	
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ____ 4. CFN numbers ____ 1 CTL Active	✓	
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified ✓ 3. If sterile product: Aseptic fill ____ / Terminal sterilization ____ 4. Filter validation (if aseptic fill) ____ 5. Reprocessing Statement ✓	✓	

(b) (4)

Sec. XII	In-Process Controls 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓	
Sec. XIII	Container 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and supplier's address ✓	✓	
Sec. XIV	Controls for the Finished Dosage Form 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓	✓	
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on Stability records the same as the test batch ✓	✓	
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	✓	
Sec. XVII	Environmental Impact Analysis Statement	✓	

(b) (4)

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) _____ 2. Debarment Certification (original signature) ✓ 3. List of Convictions statement (original signature) ✓	✓	

Reviewing CSO/CST [signature] Date 7/2/01

Recommendation: FILE REFUSE to FILE

Supervisory Concurrence/Date [signature] 02-JUL-2001

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD _____ for consult

Type of consult:

Comments regarding the ANDA:

(b) (4)

*① C+C

ok ✓

(b) (4)

② DMF-Type-II - Firm has stated no DMF # assigned in letter, but have mentioned DMF # in summary. Firm has to provide a DMF authorization for DMF # 15385

o/c ✓

o/c ✓

③ Provide cGMP for (b) (4) a signature.

Revised 12/99 - v:\division\revsupp\regsupp\chklst

ANDA 40-436

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

JUL - 2 2001

Dear Madam:

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

Reference is made to the telephone conversation dated July 2, 2001 and to your correspondence dated July 2, 2001.

NAME OF DRUG: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

DATE OF APPLICATION: May 31, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 5, 2001

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) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-436
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief, RSB Davis 02-JUL-2001 date
HFD-615/PPatel,CSO Patel date 7/2/01
Word File
V:\Firmsam\Mallinckrodt\ltrs&rev\40436.ACK
F/T EEH 07/02/01
ANDA Acknowledgment Letter!