CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-419 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 7/31/01 **Action Date:** 01/31/02

HFD 120 **Trade and generic names/dosage form:** Methylin (methylphenidate HCl) Oral Solution

Applicant: Mallinckrodt, Inc. **Therapeutic Class:** ADHD Treatment

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: ADHD

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply:** X **Partial Waiver** ____ **Deferred** ____ **Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg** ____	**mo.** ____	**yr.** ≤ 6 ____	**Tanner Stage** ____
Max ____	**kg** ____	**mo.** ____	**yr.** ____	**Tanner Stage** ____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr.** $\geq$**6**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr.** $\leq$ **17**	**Tanner Stage_____**

Comments:
Approved labeling allows for usage $\geq$ **6 years**

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: ____narcolepsy_____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: __X__Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg____**	**mo.____**	**yr. ≤ 6____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.** ≥ 6 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** ≤ 17 **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anna-Marie Homonnay
12/19/02 10:26:37 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 19, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approval action for Methylin Oral Solution (methylphenidate oral solution, 5 mg/5mL and 10 mg/5mL), for ADHD and narcolepsy.

TO: File NDA 21-419
[Note: This memo should be filed with the 10-31-02 response to our 5-31-02 approvable letter.]

This NDA for an oral solution of methylphenidate was submitted as a 505(b)(2) application, and included the results of 2 pk studies in adults. The original application was reviewed by OCPB, CMC, the pharmacology/toxicology group and the clinical group. We issued an approvable letter 5-31-02, identifying several issues that needed resolution prior to final approval:

-Trade Name: We asked them to change the name from Methylin — to simply Methylin Oral Solution.

-Response: They have accepted this revised name.

-Container Labeling: We made several suggestions for changes to container labeling to minimize the risk for errors.
-Response: They have made the requested changes.

-New Impurities: We noted the presence of 2 new impurities at levels requiring qualification, and asked for the tox studies needed to qualify them.
-Response: Additional stability data have shown that the impurities in question (A & B) each remain below the ——— up to 18 mo. Thus, they have proposed an 18 mo expiry, and they have agreed to do limited tox testing within 12 months postapproval (14 day general tox and 2 in vitro gentox assays). Ed Fisher, Ph.D., from the pharm/tox group has accepted this plan.

APPEARS THIS WAY
ON ORIGINAL

-Expiry: We indicated that their stability data supported only an 18 month expiry, rather than

-Response: They have accepted the 18 month expiry (see 12-16-02 review by Donald Klein, Ph.D., from CMC).

-Labeling Changes: We asked them to adopt several changes in pharmacokinetics subsection of Clinical Pharmacology.
-Response: They have made the requested changes (see 11-13-02 review by Wen-Hwei Chou, Ph.D., from OCPB). In addition, we have asked and the sponsor has agreed to further update the labeling to bring it into conformity with other methylphenidate products.

Conclusions and Recommendations
-I feel that sufficient information has been provided to justify an approval action, with the agreed upon final labeling.

cc:
Orig NDA 21-419
HFD-120/DivFile
HFD-120/TLaughren/RKatz/RGlass/AHomonnay

DOC: NDA21419.02

APPEARS THIS WAY
ON ORIGINAL

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/s/

Thomas Laughren
12/19/02 10:55:29 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 30, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approvable action for Methylin — (methylphenidate oral solution, 5 mg/5mL and 10 mg/5mL), for ADHD and narcolepsy.

TO: File NDA 21-419
[Note: This memo should be filed with the 7-31-01 original submission.]

This NDA for an oral solution of methylphenidate was submitted as a 505(b)(2) application, and included the results of 2 pk studies in adults. The application was reviewed by OCPB, CMC, the pharmacology/toxicology group and the clinical group.

OCPB

-This NDA included the results of 2 single dose bioequivalence studies in normal adults, i.e., 610 and 722. Study 610 compared MPH — (the 10 mg/mL solution) with Ritalin tablets and the Methylin CT (compressed tablet), showing bioequivalence among all three. Study 722 compared MPH — (the 10 mg/mL solution), fasted and fed, with Ritalin tablets (fed), showing that food delayed Tmax by about 1 hour and increased Cmax by about 13% and AUC by about 25%. OCPB has also concluded that the sponsor's request for a waiver of the lower strength (5 mg/mL) is acceptable, and the NDA is approvable, from their standpoint. However, they have asked that certain pk information from studies 610 and 722 be included in the Methylin — labeling, along with information from the literature regarding pk, and I agree. Their proposed language will be included in the approvable letter.

CMC

-The one CMC issue that complicates the decision for this NDA is the finding of new impurities for this product, i.e., — methylphenidate interaction product. They have set specifications for each of these at —, whichever is lower. Unfortunately, this impurity increases over storage time, exceeding the limits at about 6 months. Based on this finding, the CMC group has recommended an expiry of 18 months rather —

-One other issue is the name, Methylin [redacted] OPDRA objects to the modifier [redacted] They have recommend "Methylin Oral Solution" as an alternative. In addition, OPDRA has some recommendations for changes to the container label.

Pharmacology/Toxicology:

-The threshold for identification of an impurity is 0.2% and for qualification for an impurity is 200 μg (for the 60 mg MRHD). After 6 months at 40C/75%RH, these impurities were present at [redacted] Combining the [redacted] gives a dose approaching [redacted] for the [redacted] impurity. Consequently, the pharmacology group has recommended that these impurities need to be qualified before this product can be approved. They have recommended a minimum of a 1-month general toxicology study in 1 species, gentox, and segment 2 study in 1 species. In addition, they have recommended some minimum receptor assays to develop some basic knowledge about the possible activity of this impurity.

Clinical

-Approximately 60 normal adults were exposed to Methylin [redacted] in the two PK studies conducted as part of the development program for this product. No serious or unexpected adverse events were observed. Dr. Glass has recommended that we ask for safety studies of this new formulation in pediatric patients. However, the rationale for this request is unclear, and I am not in favor of asking for such studies in the absence of any clear justification. The possibility of requesting studies of the impurities in human subjects was also raised, however, I am also not inclined to think that such a request is adequately justified. The study would have to be quite large to rule out serious risk at any reasonable level, and I feel the animal studies should adequately serve this purpose.

Labeling

-As noted, we will request that certain PK information pertinent to this product be included in the labeling for this product, and the CMC information that is specific to this product will also distinguish it from the reference product. Dr. Glass has asked for far more extensive changes, including most other sections of labeling. However, until we implement such changes for Ritalin, the reference product, I think it would be difficult to insist on such changes for this product; thus, I do not agree with this recommendation.

Pediatric Rule

-The sponsor has requested, and Dr. Glass has also recommended, that we defer the requirement for studies in children under 6, under the Pediatric Rule. However, our current DNDP policy on studies in children under 6 is to not issue written requests for such studies, given that there remains uncertainty about (1) the diagnosis of ADHD in this younger population, (2) how to reliably make the diagnosis, even if it could be considered a legitimate entity, and (3) how to assess patients with this condition, and otherwise efficiently conduct these studies. Given that we are denying PPSRs for such studies, I think we should be waiving such studies, and not deferring them. In fact, a large NIMH study of methylphenidate in ADHD (PATS) is just getting underway. If this study is successful in demonstrating the legitimacy and feasibility of conducting such studies, and demonstrates a treatment benefit, it would be possible, in my view, to

extrapolate from the results of this study to all other methylphenidate formulations, making the conduct of any additional studies unnecessary.

Conclusions and Recommendations

-I feel that sufficient information has been provided to justify an approvable action, however, final approval would depend on the sponsor's completion of the requested toxicology studies and of the sponsor's acceptance of our proposed labeling.

cc:
Orig NDA 21-419/Methylin
HFD-120/DivFile
HFD-120/TLaughren/RKatz/RGlass/AHomonnay

DOC: NDA21419.01

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
5/30/02 10:59:46 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 18, 2002

To: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120
/S/

Through: Deborah B. Leiderman, M.D.
Director, Controlled Substance Staff
HFD-009

From: Ann-Kathryn Maust, M.D. A-KM
Controlled Substance Staff, HFD-009

Subject: CSS Consultation for NDA 21-419, Methylin [redacted] (methylphenidate oral solution)
Sponsor: Mallinckrodt

Background

HFD-120 requested that CSS evaluate the proposed abuse potential section of the Methylin [redacted] labeling.

Recommendations

CSS recognizes that incorporation of some of the recommended changes may require revision of the labels for other methylphenidate products.

1. In the Description section, it would be more accurate to describe the drug as a CNS stimulant, rather than as a "mild" stimulant. Whether the drug's effects are "mild" or otherwise varies among individuals as well as with dose. (Current labeling for the following drugs describes methylphenidate as a mild CNS stimulant: Metadate ER, Methylin tablets, Methylin ER tablets, Ritalin, Ritalin SR. However, the labeling for Metadate CD, Concerta regular release, and Concerta ER describes methylphenidate as simply a CNS stimulant.)

2. In the Clinical Pharmacology section, similarly describe methylphenidate as a stimulant, rather than a "mild" stimulant.

3. The first paragraph under Indications and Usage appears to contain outdated information and could be deleted.

4. The phrase "emotional lability" in the next paragraph should be removed, as this characteristic is not part of the DSM-IV-TR diagnostic criteria for ADHD.

5. Under Special Diagnostic Considerations, change "Characteristics commonly reported include..." to "Characteristics that may be associated with ADHD include..." because the characteristics listed are not absolute characteristics of ADHD and are not all "commonly reported."

6. In the Adverse Reactions section, change "instances of abdominal liver function" to "instances of abnormal liver function."

7. In the Drug Abuse and Dependence section, change the first sentence to "Methylin should be given cautiously to patients with a history of drug abuse or alcoholism, because such patients may increase dosage on their own initiative." If this sentence is not changed, the implication is that often "emotionally unstable" patients have problems with drug abuse. "Drug dependence" should be changed to "drug abuse" because people can be physically dependent without having a problem with abuse or addiction.

8. Insert the following sentence after the sentence noted in number 7. "However, physicians should monitor all patients for signs of abuse and dependence and should carefully monitor the amount of Methylin that is dispensed."

9. In the next sentence, either "marked" or "severe" should be deleted because the use of both terms is redundant. In addition, the term "psychic" should be removed because dependence can also be physiologic.

10. In the same section, the sentence that begins with "Careful supervision..." is unclear. The second part of this sentence should be changed to "...since depression as well as other problems can be unmasked."

BRIEF MEETING MINUTES

DATE: October 2, 2001
NDA: 21-419
LOCATION: Woodmont II, Conference Room E
DRUG: methylphenidate hydrochloride oral solution
INDICATION: attention deficit disorder
PARTICIPANTS:
Russell Katz, MD; Thomas Laughren, MD; Roberta Glass, MD; Barry Rosloff, PhD; Ed Fisher, PhD; Robert Seevers, PhD; Christy John, PhD; Ramana Uppoor, PhD; Wendy Chow, PhD

BACKGROUND: In accordance with a previous agreement within the Agency during a meeting on April 20, 2000, between representatives of OGD and ORM concerning the pediatric rule, Mallinckrodt, Inc. has submitted this NDA as a 505(b)(2) application instead of as a 505(j) application via the ANDA suitability petition route. The suitability petition was denied by OGD due to the pediatric rule. This was the standard filing meeting for this application.

DISCUSSION:

Chemistry: application is fileable.

Pharm/Tox: application is fileable. The reproductive section of the labeling will be modeled after the approved labeling for Ritalin LA® Extended-release Capsules. Consultation should be obtained from the CDER Controlled Substances Staff regarding the labeling.

Biopharmaceutics: application is fileable. An inspection of the fasting bioequivalence study will be requested from DSI.

Clinical: Acceptable for filing.

ACTION ITEMS:

Sponsor should be informed of the filing decision. Consults should be obtained from: OPDRA for the tradename, CSS regarding the product labeling, and DSI for a clinical inspection.

Anna Marie Homonnay
Project Manager

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 2, 2001	**DUE DATE:** December 31, 2001	**OPDRA CONSULT #:** 01-0211

TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Anna Marie Homonnay
Project Manager
HFD-120

PRODUCT NAME: Methylin [redacted] (Methylphenidate HCL oral solution; 5 mg/5 mL and 10 mg/5 mL) **NDA #:** 21-419	**NDA SPONSOR:** Mallinckrodt, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary name "Methylin [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA objects to using any modifier for this product; we recommend that the sponsor label the proposed product as "Methylin Oral Solution."

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

A

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA Request
HFD-400
Parklawn Bldg/Room 15B-03
Attention: Sammie Beam, Project Manager

FROM: Division of Neuropharmacological Drug Products
HFD-120
Woodmont II Bldg

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Oct. 2, 2001		21-419		7/31/01

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Methylin Oral Solution			May 2, 2002

NAME OF FIRM: Mallinckrodt, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Please find attached the labeling for pending NDA 21-419. If you should have any questions, please call Ms. Anna Marie Homonnay at: 594-5535**

Thank You

IATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-419

Mallinckrodt Inc.
Attention: Ronald Groman
Manager, Regulatory Affairs
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Mr. Groman:

Please refer to your July 31, 2001, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylin — (methylphenidate hydrochloride) Oral Solution, 5 mg/5 mL and 10 mg/5 mL.

We also refer to the April 15, 2001, telephone conference with FDA regarding CMC issues.

We are reviewing the chemistry sections of your NDA and, as discussed on April 15, 2001, have identified some additional issues needing further clarification which are listed below. We request a prompt written response in order to continue our evaluation of your NDA.

[redacted]

[redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Acting Chemistry Team Leader
Psychiatric Drug Products
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hasmukh Patel
4/23/02 03:08:26 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-419

Mallinckrodt Inc.
Attention: Ronald Groman
Manager, Regulatory Affairs
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Mr. Groman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Methylin [redacted] (methylphenidate hydrochloride) oral solution 5 mg/5 mL and 10 mg/5 mL

Review Priority Classification: Standard (S)

Date of Application: July 31, 2001

Date of Receipt: August 3, 2001

Our Reference Number: NDA 21-419

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 3, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 2, 2002.

APPEARS THIS WAY
ON ORIGINAL

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 25, 2001

TO: Director, Investigations Branch
Kansas City District Office
11630 W. 80th St. - P.O. Box 15905
Lenexa, Kansas 66285-5905

Director, Investigations Branch
Dallas District Office
3310 Live Oak Street
Dallas, TX 75204

FROM: C.T. Viswanathan, Ph.D. [redacted] 10/25/01
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2002 **High Priority CDER User Fee NDA**, Pre-approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-419
DRUG: Methylin [redacted] (Methylphenidate Hydrochloride Oral Solution) 5 mg/5 ml; 10 mg/5 ml
SPONSOR: Mallinckrodt Inc.
St. Louis, Missouri

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study. **Due to the user fee deadline, these inspections must be completed by March 1, 2002.**

Protocol: 1137-00-610, An Open-Label, Randomized, Three-Way Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/ml Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions (Study #610).

Clinical Site:

Clinical Investigator:

Please check the batch numbers of both the test and the reference drug formulations used in the study with the descriptions in documents submitted to the Agency. If study formulations have not been submitted to the Agency previously, samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited, including 100% of the informed consent forms. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content.

Analytical Site:

Project Director:

Instrumentation: LC/MS/MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms submitted to the Agency should be compared with the original documents at the firm. The method validation and the actual assay of plasma samples, as well as the variability within and between runs, Q.C., stability, the number of repeat assays of subject plasma samples, and the reasons for such repetitions, if any, should be examined. Acceptance of specific repeated results should be examined for consistency with the SOP. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the files of communication between the sponsor and the analytical site should be examined for their content.

Following identification of the investigator, background materials will be forwarded directly. **A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspections.**

Headquarters Contact Person: Jacqueline A. O'Shaughnessy, Ph.D.
(301) 827-5463

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FACTS 256558

[redacted]

cc:
HFA-224
HFD-45/RF
HFD-48/O'Shaughnessy(2)/CF
HFD-120/Homonnay
HFR-SW1540/Joel Martinez
HFR-SW350/Greg Dixon
Draft: JAO 10/25/01
Edit: MKY
DSI:5400 O:\BE\assigns\bio21419.doc

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MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

NEW DRUG APPLICATION

July 31, 2001

Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: 505(b)(2) New Drug Application for Methylin® —
(Methylphenidate Hydrochloride Oral Solution)
5 mg/5 mL and 10 mg/5 mL CII**

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this 505(b)(2) New Drug Application under 21 C.F.R. §314.70(a)(2)(i). This NDA is for Methylin® — (Methylphenidate Hydrochloride Oral Solution) 5 mg/5 mL and 10 mg/5 mL CII, a clear, colorless to —— solution with a grape odor. It is a schedule II prescription drug indicated for treatment of Attention Deficit Disorders and Narcolepsy. Methylin® — (Methylphenidate Hydrochloride Oral Solution) 5 mg/5 mL and 10 mg/5 mL CII will be held, manufactured, processed, packaged, labeled, tested for release and stability and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

For ease of reference, the entire application is numbered sequentially in the bottom right corner with the volume number preceding the period and the page number of that volume following the period. If necessary, the pagination uses alphabetical sequencing following a number.

Three copies of the application have been filed: an archival copy (in blue folder), a technical review copy (in red folder) and a field copy (in maroon folder). Additionally, two separately bound copies of the analytical methods (in red folders) and a separate copy of the nonclinical pharmacology and toxicology section (in yellow folder), human pharmacokinetics and bioavailablity section (in orange folder) and clinical data section (light-brown folder) have been filed. The technical review copy, field copy and separately bound copies are identical to

the archival copy and a certification attesting to this is provided in the Field Copy Certification.

Some NDA sections were not applicable to this 505(b)(2) NDA application and thus were not included herein. The NDA sections that were neither bound separately nor included in this application are the Microbiology Section and the Statistical Evaluation of Clinical Data Section. The Microbiology Section does not apply to this 505(b)(2) application for methylphenidate hydrochloride oral solution. The statistical analysis of the pharmacokinetic and safety data from the bioequivalence studies is included in the respective study reports in Section VI.

Since the product will be manufactured, held and distributed at Mallinckrodt's Hobart, New York facilities, a field copy has been sent to the Buffalo District Office.

This hard copy is being sent concurrently via United Parcel Service.

Correspondence related to this submission should be addressed to Ronald T. Groman, Mallinckrodt Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, Missouri 63134.

Sincerely,

Ronald T. Groman

Ronald T. Groman
Manager, Regulatory Affairs
Phone: (314) 654-6060
Fax: (314) 654-6496

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partment of Health and Human Services
blic Health Service
od and Drug Administration

Request for Consultation

ate 8/30/2000

To: HFD-860/Baweja

From: Neuropharmacology, HFD-120

IND/NDA No. pre-NDA

DELIVERED AUG 3 0 2000

Drug Name methylphenidate HCl

Trade Name

Sponsor Mallinckrodt Inc.

Indication ADHD

ype of Document Request for FDA comment

)ate of Document 8/29/2000

Reason for Request

Ray,
Sponsor would like to submit a 505(b)(2) application for methylphenidate chewable tablets and oral solution. There was the issue of the pediatric rule a ' deferral of pediatric studies and the suitability petition process which have been addressed at a meeting (minutes attached).

Please comment whether from a biopharm perspective, 1)their proposed biopharm program is adequate 2) they can waiver the lower dosage strengths (they did not submit a formulation comparison).

Thank You

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/S/	( ) Mail (/) Hand
ignature of Receiver	Signature of Deliverer
/S/ 8/31/00	/S/

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 11 2000

Mallinckrodt, Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134

Dear Mr. Keller:

Thank you for writing to the Center for Drug Evaluation and Research (CDER). This is in response to your letter of March 22, 2000.

In your letter, you expressed concern about the Agency's policy on pediatric data for ANDA drugs subject to suitability petitions. I understand that our policy has raised some concern among industry and various trade organizations. Please be aware that we are committed to assuring that safe and effective drugs are available for all consumers, including children. We also are committed to encouraging new innovations, such as new dosage forms. We appreciate your position and will consider your comments as we continue to assess this complex issue.

I am aware that you have been contacted by the Division of Neuropharmacological Drug Products regarding the necessary studies for the use of methylphenidate in children.

I would like to thank you again for sharing your comments and observations on this matter. Please be assured that the FDA will consider all aspects of this issue as it pertains to public health.

Sincerely,

/S/

Janet Woodcock, M.D.
Director,
Center for Drug Evaluation and Research

CDER log number: 2000-495
FDA trac number:

cc:

R/D: Kinsey 5/10/00
Concur: KB 5/11/00

Cc:

HFD-120 (Homonnay)
HFD-101
HFD-002
HFD-600 (R. Hassall)

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stated that the Division would not assure Mallinckrodt that the query would be answered. Likewise, no time line was given for an Agency response even if it decided to respond. This approach does not appear to be a reliable means of gaining Agency input to a plan of action for these drug products.

Submitting an IND appears to be the only viable option for seeking Agency comments to a study plan. By regulation, FDA has thirty days to respond to an IND or the study may be initiated without further delay. However, FDA generally attempts to provide comments to the proposed study plan within the thirty-day period. This approach does not provide the interaction and dialogue that can be gained from a face-to-face meeting, but it should provide guidance and recommendations to help determine an acceptable approach of addressing pediatric study issues. It would be reasonable to submit a single IND for either the chewable tablet or liquid dosage form since the clinical approach should be the same for both dosage forms. It should be noted that if the Agency rejects the initial proposal contained in an IND, subsequent amendments to the IND are not subject to the 30-day response deadline. Therefore, one cannot assume that a firm plan of action for studies, clinical or pharmacokinetic, will be established within thirty days of submission of the IND.

It is unfortunate that the Agency is restricting its meetings at this time to only the highest priority projects. Nevertheless, it appears that there is an opportunity to seek limited guidance through an IND. To do so, it will be necessary to define specific pharmacokinetic or clinical approaches for establishing safety and efficacy in pediatric patients, propose age groups to be studied and determine potential end points for any proposed clinical study.

Please do not hesitate to contact me if I can be of further assistance.

Sincerely,

S

cc:

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