CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-475

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

tyco
Healthcare

Mallinckrodt

Jeffrey S. Boone, J.D.
Assistant General Counsel
direct: 1 (314) 654-8955
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Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis, MO 63134

2001 December 17

PATENT INFORMATION

Methylin® CT methylphenidate hydrochloride chewable tablets
2.5 mg, 5 mg, and 10 mg

The applicant makes the following submission in connection with its application under section 505(b)(2) of the act for Methylin® CT methylphenidate hydrochloride chewable tablets, 2.5 mg, 5 mg, and 10 mg.

Patent Information (21 CFR 314.50(h) and 314.53(c)(3))
The applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Mallinckrodt Inc.

by: Jeffrey S. Boone

Jeffrey S. Boone, J.D.
Assistant General Counsel

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tyco
Healthcare

Mallinckrodt

Jeffrey S. Boone, J.D.
Assistant General Counsel
Patents and Trademarks

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

Phone: 314.654.8955
Fax: 314.654.3156
jsboone@mkg.com

2001 December 17

PATENT AND EXCLUSIVITY CERTIFICATION
Methylin® CT methylphenidate hydrochloride chewable tablets 2.5 mg, 5 mg, and 10 mg

The applicant makes the following certifications in connection with its application under section 505(b)(2) of the act for Methylin® CT methylphenidate hydrochloride chewable tablets, 2.5 mg, 5 mg, and 10 mg. These certifications are based on information found in the 21st Edition of *Approved Drug Products with Therapeutic Equivalence Evaluations*.

Patent Certification (21 CFR 314.50(i)(1)(ii))
In the opinion and to the best knowledge of Mallinckrodt Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Exclusivity Statement (21 CFR 314.108(b))
According to information published in the list, the reference listed drug is not entitled to any period of exclusivity (or any such periods have expired and are no longer listed).

Mallinckrodt Inc.

by: Jeffrey S. Boone

Jeffrey S. Boone, J.D.
Assistant General Counsel

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Office of Drug Safety

Memo

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

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Anna Marie Weikel
Project Manager
HFD-120

Date: April 1, 2003

Re: ODS Consult 02-0189-1; Methylin Chewable Tablets (Methylphenidate Chewable Tablets) 2.5 mg, 5 mg, 10 mg; NDA 21-475.

In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), DMETS reviewed the proposed container labels and package insert labeling of Methylin Chewable Tablets, for possible interventions that may help minimize medication errors.

Methylin Chewable Tablets was originally reviewed on October 9, 2002 (see ODS consult 02-0189). Since the completion of this review, DMETS has not identified additional proprietary names with look-alike or sound-alike potential that would render the name objectionable.

In reviewing the container labels and package insert labeling for Methylin Chewable Tablets, DMETS did not identify any safety issues. Therefore, DMETS recommends the approval of the proposed labels and labeling.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-7847.

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

/s/

Denise Toyer
4/4/03 02:47:50 PM
PHARMACIST
for Alina Mahmud

Carol Holquist
4/4/03 02:50:19 PM
PHARMACIST

MODE = MEMORY TRANSMISSION START=MAR-20 17:49 END=MAR-20 17:50

FILE NO.= 176

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-FDA/DNDP -

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FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
5600 FISHERS LANE [HFD-120]
ROCKVILLE, MARYLAND 20857
FAX: [301] 594-2858/594-2859
COVER SHEET

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at [301]-594-2850 or return it to us at the above address by mail. Attention [HFD-120]. Thank you in advance.

DATE: March 20, 2003

TIME: _____

PLEASE DELIVER THE FOLLOWING PAGES TO:

Mr. Ron Gronon, Regulatory Affairs

FAX NUMBER: (314) 654-6496

FROM: Ms. Anna Marie H Wendel

Total number of pages, including cover page: 2

If you do not receive all pages or have any problems with receiving, call [301]594-2850.

MESSAGE:
This relates to the previous fax and just indicates what the changes are. Let's discuss however. (301) 594-5535

Note: Unless specified, the revised labeling is acceptable. Only the sections that need changes are incorporated here. Strikethrough indicates deletion, underline indicates addition.

Absorption

Methylin chewable tablets are readily absorbed. Following oral administration of Methylin chewable tablets, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin chewable tablets have been shown to be bioequivalent to Ritalin ® tablet. The mean Cmax following a 20mg dose is approximately ~~–~~ 10 ng/ml.

Food Effect

In a study in adult volunteers to investigate the effects of a high- fat meal on the bioavailability of Methylin chewable tablets at a dose of 20mg, the presence of food delayed the peak by approximately 1 hour (~~–~~ 1.5 hours, fasted and ~~–~~ 2.4 hours, fed). Overall, a high fat meal increased the ~~—~~ AUC of Methylin chewable tablets by about ~~—~~ 20 %, on average. Through a cross- study comparison, the magnitude of food effect ~~—~~ is found to be comparable between the Methylin chewable tablets and Ritalin, the immediate release tablet.

Under Metabolism and excretion section:

The pharmacokinetics of the Methylin chewable tablets have been studied in healthy adult volunteers. The mean terminal half- life ($t_{1/2}$) of methylphenidate following administration of 20mg Methylin chewable tablets ($t_{1/2}$ = ~~—~~ 3 hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate- release tablets) ($t_{1/2}$ = 2.8 hours) in healthy adult volunteers.

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FILE NO.= 172

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********** - ***** - 3015942859- **********

FOOD AND DRUG ADMINISTRATION
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DATE: March 20, 2003

TIME: _____

PLEASE DELIVER THE FOLLOWING PAGES TO:

Mr. Ron Gromon, Regulatory Affairs, Mallinckrodt, Inc.

FAX NUMBER: (314) 654-6496

FROM: Ms. Anna Marie H. Weikel

Total number of pages, including cover page: 3

If you do not receive all pages or have any problems with receiving, call [301]594-2850.

MESSAGE:

_____

_____

_____

_____

Attachment 1: OCPB labeling comments in the review dated 8/28/2002

(2) Labeling:
We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in the current label for the reference listed drug Ritalin® as well as your proposed label for Methylin CT. We request you to update the labeling of Methylin CT to incorporate the above information from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products, we suggest following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

Clinical Pharmacology
(double strikethrough indicates deletion; underline indicates addition; bracket indicates explanation with reference number in the submission, which should not be included in final label)

Methylphenidate is a racemic mixture comprised of the *d-* and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer. [Patrick & Markowitz 1997, class labeling text]

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in ~~—~~ humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. [#66, Patrick et al 1987]

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

Pharmacokinetics:
Absorption
Methylin CT is readily absorbed. Following oral administration of Methylin CT, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin CT has been shown to be bioequivalent to Ritalin® tablet. Mean Cmax following a 20mg dose is approximately 10 ng/ml. [study #610]

Food Effect:
In a study in adult volunteers investigating the effects of a high-fat meal on the bioavailability of Methylin CT at a dose of 20mg, the presence of food delayed the peak concentrations by approximately 1 hour (1.5 hours, fasted and 2.4 hours, fed). Through a cross study comparison, the magnitude of food

effect is found to be comparable between the Methylin CT and Ritalin, the immediate release tablet. [study #721].

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity. [#66, Patrick et al 1987]

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose. [# 67, Faraj et al 1974]

The pharmacokinetics of the Methylin CT have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20 mg Methylin CT ($t_{1/2}$=3 hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2}$=2.8h) in healthy adult volunteers. [study #610]

Special Population:

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin CT administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin CT in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid [# 67, Faraj et al 1974]. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin CT.

Hepatic Insufficiency

There is no experience with the use of Methylin CT in patients with hepatic insufficiency.

A

7 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Thursday, August 29, 2002 11:36 AM
To: 'Ron.Groman@mkg.com'
Subject: re: NDA 21-475

Hi Ron:

Below are comments from the Office of Clinical Pharmacology and Biopharmaceutics regarding the dissolution specs. We would also be agreeable to a telephone conference to further discuss if you wish:

Dissolution specification:
The selected dissolution method is acceptable. However, we recommend a change in dissolution specification for all three strengths of Methylin CT to Q= — in 30 minutes.

Sponsor proposed specification:	Q= — in 45 minutes
Agency recommended specification:	Q= — in 30 minutes

We recommend that Q= — in 30 minutes be accepted as interim dissolution specification for all 3 strengths of Methylin CT until additional data (described below) is submitted and reviewed.

Phase IV commitment regarding dissolution specification: Submit dissolution and stability data, for production batches of all three strengths (— per strength) using sponsor proposed and agency recommended dissolution specifications (i.e. 30 and 45 minutes). These batches could be next — production batches or batches currently on stability. These data should be submitted to the agency no later than 1½ years from the date of approval of this product. The sponsor should make a Phase IV commitment to submit this data for finalization of dissolution specification.

- **Additional comment from the Chemistry:**
Setting the expiration date at the approval of this application will be based on dissolution data at 45 minutes. But when the Phase IV commitment has been fulfilled which means you have generated sufficient stability data including dissolution at 30 minutes, the expiration date may have to be revised based on the dissolution stability data at 30 minutes

---

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Regulatory Affairs Manager
(301) 594-5535

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-475

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® CT (methylphenidate hydrochloride) Chewable Tablets, 2.5 mg, 5.0 mg and 10 mg

Review Priority Classification: Standard (S)

Date of Application: December 19, 2001

Date of Receipt: December 20, 2001

Our Reference Number: NDA 21-475

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 February 20, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 20, 2002.

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

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
1/9/02 11:42:05 AM