CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-475

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-475

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

Dear Mr. Groman:

Please refer to your new drug application (NDA) dated December 19, 2001, received December 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylin® (methylphenidate hydrochloride) Chewable Tablets, 2.5 mg, 5.0 mg and 10 mg.

We acknowledge receipt of your submission dated February 14, 2003.

The February 14, 2003, submission constituted a complete response to our October 18, 2002, action letter.

This new drug application provides for the use of Methylin® (methylphenidate hydrochloride) chewable tablets for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) and narcolepsy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling, for the package insert with the agreed upon changes. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-475." Approval of this submission by FDA is not required before the labeling is used.

We also encourage you to develop a patient package insert for this product to be consistent with the labeling for other recently approved products for the treatment of ADHD. This may be submitted as a labeling supplement post-approval.

Chemistry Issues

1. A 24 month expiry is granted for Methylin® Chewable Tablets.

2. We have not completed validation of the regulatory methods. However, we expect to continue to work with you to resolve any problems that may be identified.

Biopharmaceutics Issues

The following agreed upon interim dissolution specification has been approved for all three strengths of Methylin® Chewable Tablets:

Apparatus 1: 100 rpm
Medium: 900 mL water
Q value: [redacted] in 30 minutes

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
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/

Russell Katz
4/15/03 08:51:47 AM

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APPROVABLE LETTER(S)

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:

Please refer to your new drug application (NDA) dated December 19, 2001, received December 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylin® CT (methylphenidate hydrochloride) Chewable Tablets, 2.5 mg, 5.0 mg and 10 mg.

We acknowledge receipt of your submissions dated February 13; April 10 and 18; August 29; September 6, 10, 16, 24 and October 15, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry Issues

1. Please provide the finalized release specifications for — grape flavor when they become available.

2. For the proposed drug product specifications, we have the following comments:

a) With regards to the specification for — appears to be appropriate for Methylin CT; however, you have not demonstrated — — you have proposed and there is no release or stability data for — . We also note that all — exhibit batches were analyzed using — method. Therefore, you should still use the — as the interim test method. However, post-approval — should be performed using both — methods. When sufficient release and stability data have been accumulated, you may submit the data and finalize the specification — using the — method.

In addition, you should propose an upper and lower limit for — specification using the — method. —

b) Your proposed specification of NMT — for the — mpurity should be tightened to NMT — or, you may provide data showing that this impurity has been qualified to the — limit.

c) We recommend tightening the specification for the — impurity from NMT — to NMT — based on the batch data provided.

d) You should tighten the specification for the Other Related Substances from NMT — to NMT —, in accordance with the ICH Q3B guidance/identification threshold.

e) Please provide the LODs for the — — — by the related substances — method

f) Your proposal to use Q= — at 30 minutes dissolution specification is acceptable. Therefore, no intermediate dissolution specification is necessary. Please provide dissolution data (release/stability) demonstrating that the specification limit of Q= — at 30 minutes can be met.

3. You did not propose a microbial specification for this drug product. Please provide a justification, with relevant test data, for not setting a specification for microbial limits.

4. Please provide updated drug product stability data.

5. You have indicated that you plan to put at least — of each package size into the long term stability program. Please clearly indicate the number of batches you plan to put on stability annually.

6. Please change the storage statement on both the package insert and the bottle label to the following:

   'Store at 25° C (77° F); excursions permitted to 15° C - 30 C (59° F - 86° F) [see USP Controlled Room Temperature].'

Labeling Issues

1. With regards to your proposed trade name, —

— Therefore, DMETS recommends that you label the product simply as 'Methylin Chewable Tablets' which is a recognized compendial dosage form descriptor. If you disagree with this recommendation, please provide a justification, or you may request a teleconference to further discuss this with the Division and DMETS.

CONTAINER LABELING

In order to minimize the risk for medication errors, DMETS recommends the following:

- Decrease the prominence of the manufacturer's name in relation to the proprietary name.
- Differentiate the two strengths with the use of different colors since the proposed colors seem very similar.

2. Based upon the information submitted, including the two studies and the literature, we suggest the following relevant pharmacokinetic information be added to the "Clinical Pharmacology" section of the labeling:

(double strikethrough indicates a deletion, underline indicates an addition)

Clinical Pharmacology

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.

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.

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 is readily absorbed. Following oral administration of Methylin peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin has been shown to be bioequivalent to Ritalin® tablet. The mean Cmax following a 20mg dose is approximately g/ml.

Food Effect:
In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of Methylin at a dose of 20mg, the presence of food delayed the peak by approximately 1 hour (hours, fasted and hours, fed). Overall, a high fat meal increased the of Methylin by about , on average. Through a cross-study comparison, the magnitude of is found to be comparable between the Methylin

— and Ritalin, the immediate release tablet.

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.

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.

The pharmacokinetics of the Methylin AQ oral solution have been studied in healthy adult volunteers. The mean terminal half-life (t1/2) of methylphenidate following administration of 20mg Methylin — (t 1/2 = — nours) is comparable to the mean terminal t1/2 following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) (t 1/2 =2.8h) in healthy adult volunteers.

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

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

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

Renal Insufficiency:
There is no experience with the use of Methylin — 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. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin —

Hepatic Insufficiency:
There is no experience with the use of Methylin — in patients with hepatic insufficiency.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final

print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
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/

Russell Katz
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