CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-419

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 July 31, 2001, received August 2, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylin® Oral Solution (methylphenidate hydrochloride oral solution), 5 mg/5 mL and 10 mg/5 mL.

We acknowledge receipt of your submission dated October 31, 2002.

The October 31, 2002, submission constituted a complete response to our May 31, 2002 action letter.

This new drug application provides for the use of Methylin® Oral Solution (methylphenidate hydrochloride oral solution) 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 submitted Final Printed Labeling (FPL) dated October 31, 2002, for the package insert. Accordingly, the application is approved effective on the date of this letter.

Post Marketing Commitments

We remind you of your post marketing study commitments in your submission of October 31, 2002, to further qualify the impurities, (b)(4)---------- These commitments are listed below--

1. Genetic toxicity testing, Ames test and chromosomal aberration test:

   Final Report: Within 12 months of NDA approval

2. 14-Day General Toxicity Study in rats:

   Final Report: Within 12 months of NDA approval.

Please submit all clinical protocols to your IND for this product; and, all non-clinical and chemistry protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), please include a status summary of each commitment in your annual report to this NDA. This status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled, 'Postmarketing Study Protocol', 'Postmarketing Study Final Report', or 'Postmarketing Study Correspondence'.

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. An 18 month expiry is granted for Methylin® Oral Solution.

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.

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., 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

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Application Number 21-419

APPROVABLE LETTER

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 new drug application (NDA) dated July 31, 2001, received August 3, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylin [redacted] (methylphenidate hydrochloride) Oral Solution.

We acknowledge receipt of your submissions dated May 7 and 17, 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:

Clinical Issues

1. We have consulted your proposed trade name, 'Methylin [redacted] to the Office of Post-Marketing Drug Risk Assessment (OPDRA) per CDER review procedures. OPDRA objects to including the modifier [redacted] in the trade name of this product, a solution formulation, since it is not necessary in differentiating this product from the other currently available Methylin formulations, Methylin and Methylin ER Tablets. OPDRA prefers that you label the product simply as 'Methylin Oral Solution'. If you disagree with this recommendation, please provide a justification, or you may request a teleconference to further discuss this with the Division and OPDRA.

2. CONTAINER LABELING (5 mg/5 mL and 10 mg/5 mL)

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

   1. Increasing the font size so that the net quantity appears larger than the NDC numbers.

   2. Relocating the, "Each milliliter contains..." statement from the main panel to the side panel in order not to detract attention away from the strengths, 5 mg/5 mL or 10 mg/5 mL.

Pharmacology/Toxicology Issues

The chemistry review has revealed that two new impurities (referred to as "Related Substances A and B") exceeded the ICH thresholds for identification (0.2%) and qualification (200 mcg TDI for 60 mg MRHD) under accelerated conditions (Guidance for Industry: Q3B Impurities in New Drug Products). After 6 months at 40 C/75% RH, these impurities were present at levels of [redacted] These impurities were subsequently identified as products formed when [redacted] Since the new impurities [redacted] are each present at levels exceeding the qualification limit (and together could exceed a level [redacted] under conditions that could occur during the proposed shelf life, animal toxicology studies establishing their safety are needed, as discussed in the ICH Guidance on Impurities in New Drug Products. At a minimum, these should include a 1-month general toxicity study in one species, a genotoxicity screen, and a developmental toxicity study in one species.

Chemistry Issues

We note that you have requested [redacted] expiration date for this drug product. However, based upon the stability data that has been provided in the NDA, an expiration date of 18 months would be more appropriate, since Methylin [redacted] is a labile product and prone to decomposition with time in the presence of heat and humidity.

Biopharmaceutics Issues

1. Based upon available information from the current submission, including the two studies and literature, we suggest the following relevant PK information be added to the "Clinical Pharmacology" section of the labeling:

[redacted]

B

Number of Pages Redacted 1

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Draft Labeling
(not releasable

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 Health 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

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/s/

Russell Katz
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