CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

PHARMACOLOGY REVIEW(S)

May 27, 2002

Review and Evaluation of Pharmacology and Toxicology
Original NDA Review

NDA: 21-419

Sponsor: Mallinckrodt Inc.
St. Louis, MO

Received: July 31, 2001

Drug: Methylphenidate HCl Oral Solution (Methylin [redacted]

Indication: ADHD

Recommendations:

This 505(b)(2) application for an oral solution of methylphenidate relies entirely on the extensive scientific literature for supporting preclinical pharmacology, ADME, and toxicology information. This is considered adequate for the drug substance; and since no unusual excipients are used in the new formulation, there would normally be no Pharm/Tox objections to approval. However, the chemistry reviewer (Christy John), in his evaluation of the sponsor's stability data, found that two **new** impurities (referred to as "Related Substances A and B") exceeded the ICH thresholds for identification (0.2%) and qualification (200 ug 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] **in two different lots**. The impurities were subsequently identified as products formed when methylphenidate is added to [redacted]

[redacted] but its toxicity has not been examined. Since the new impurities ([redacted]) are each present at levels exceeding the qualification limit (and together could exceed a [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.

cc:
NDA (21-419)
Div File
HFD-120/BRosloff/AMHomonnay Weikel/EFisher

J.E. Fisher, Ph.D.

December 7, 2002

Review and Evaluation of Pharmacology and Toxicology
Response to Approvable Letter

NDA: 21-419

Sponsor: Mallinckrodt Inc.
St. Louis, MO

Received: November 9, 2002

Drug: Methylphenidate HCl Oral Solution (Methylin [redacted]

Indication: ADHD

Summary and Recommendations:

The only pharm/tox issue discussed in the approvable letter (dated 5/21/02) involved the need for qualification of two impurities (referred to as "Related Substances A and B") that were present at levels exceeding the ICH qualification limit under accelerated storage conditions and that the chemist thought could be reached during the proposed shelf life (see pharm/tox review dated 5/27/02). In their response, the sponsor has provided additional stability data showing that these impurities, which they have identified as the [redacted], each remained [redacted] at the 18 month interval (see chemistry review for details). They are now proposing that the expiration date be lowered [redacted] to 18 months, as recommended by the Division in the approvable letter, and that animal toxicology studies be conducted to qualify the impurities within 12 months postapproval. The studies they are proposing are two *in vitro* gentox assays (Ames and chromosomal aberration tests) and a 14-day general toxicity study in rats. They argue that there is no need for developmental toxicity testing, since the liquid formulation will rarely be used in patients of reproductive age. This is not a valid reason, unless the indicated patient population were limited to young children, which it is not. But based on the purported chemical structures of these impurities the level of concern for toxicity is fairly low, since it appears that they should be readily [redacted] in the gut, liver, and plasma. Therefore, it is recommended that the sponsor's proposal for Phase IV animal studies be accepted.

A separate issue, and one that was not addressed in the approvable letter, concerns labeling. The sponsor had previously proposed [redacted] the existing Ritalin label. However, labeling for Ritalin products has since been updated with the approval of Ritalin LA. Therefore, it is recommended that the Methylin [redacted] label be based on the updated Ritalin labeling, at least with respect to pharm/tox information (ie, Pharmacology, Carcinogenicity, Pregnancy, and Pediatric use sections).

cc:
NDA (21-419)
Div File
HFD-120/BRosloff/AMHomonnay Weikel/EFisher

J.E. Fisher, Ph.D.

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

/s/

Edward Fisher
12/18/02 10:32:38 AM
PHARMACOLOGIST

Barry Rosloff
12/18/02 01:08:03 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL