

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207960Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 207960  
Supporting document/s: 000  
Applicant's letter date: 2/4/2015  
CDER stamp date: 2/4/2015  
Product: Methylphenidate extended-release chewable  
tablets  
Indication: ADHD  
Applicant: Pfizer Inc.  
Review Division: DPP  
Reviewer: Ikram Elayan, Ph.D.  
Supervisor/Team Leader: Linda Fossom, Ph.D.  
Division Director: Mitchel Mathis, M.D.  
Project Manager: Hiren Patel, Pharm.D.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207960 are owned by Pfizer or are data for which Pfizer has obtained a written right of reference.

Any information or data necessary for approval of NDA 207960 that Pfizer does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207960.

# 1 Executive Summary

## 1.1 Introduction

This NDA is a 505(b)(2) application for the marketing authorization of methylphenidate HCl extended-release chewable tablets (ERCT) for which Methylin chewable tablets (NDA 21-475, Mallinckrodt) is the Reference Listed Drug (RLD). The product is supplied as an ERCT that contains 20 mg, 30 mg or 40 mg methylphenidate HCl USP.

## 1.2 Brief Discussion of Nonclinical Findings

No non-clinical studies were conducted or submitted under this application.

The chemistry team indicated that there was one impurity that was above the qualification threshold (NMT 1.5%) (e-mail communications with the chemistry reviewer). This impurity was identified as (b) (4) which is a significant (b) (4) (b) (4) that is present in both animals and humans. Therefore, because it is a significant (b) (4) in both animals and humans, it is considered qualified.

Also, the chemist indicated that the levels of one of the excipients (sodium polystyrene sulfonate) will be up to (b) (4) day. This compound is used as an active ingredient in the treatment of hyperkalemia at an average daily dose of (b) (4) day, which is vastly higher than the levels in this product. In addition, higher levels of this compound ((b) (4) day) were used as an inactive ingredient in a previously approved application (see NDA 202100).

In addition, the chemist indicated that in accordance with the Agency guidance "Naming of Drug Products Containing Salt Drug Substances" the primary labeled strength would need to be in terms of methylphenidate free base, rather than the hydrochloride salt. Consequently, the name and amount of each of the components (as well as an equivalency statement for the methylphenidate hydrochloride component) will need to appear elsewhere on the label and in the labeling. For the purposes of converting the HCl salt of methylphenidate (MPH) to the base form a conversion factor of (b) (4) should be applied.

## 1.3 Recommendations

### 1.3.1 Approvability

This product is approvable from a pharmacology/toxicology perspective pending labeling agreement.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

The following sections are extracted from the sponsor's proposed labeling and the changes proposed by the reviewer are provided as tracked-changes. The sponsor was asked to provide clinical data so that the label adheres to the Pregnancy and Lactation Labeling Rule (PLLR) format and the sponsor agreed to provide the data. For the nonclinical data in section 8.1, the reviewer followed the style and the changes that were implemented in Aptensio label (a class model) for the current drug even though the RLD is methylin. However, only publicly available data were used for this purpose. The embryofetal development study that was conducted for Ritalin (the RLD for Aptensio) by Novartis is publicly available [Beckman et al., Birth Defects Research (Part B): 83:489-501, 2008]; therefore data from this study were used in this label. The other data that the sponsor does not have a right of reference to or is believed not to be publicly available was removed from the label (for all sections of the label). Comments were sent to the sponsor to either provide a right of reference to the data or to provide a publicly available source for the data.

**Note:** safety margins were **not** recalculated to reflect the expression of the dose based on the base instead of the salt form since this difference is minimal (20%).

## 8.1 Pregnancy

### Risk Summary

There are

(b) (4)

No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to rats and rabbits during organogenesis at doses 2 and 11 times, respectively, the maximum recommended human dose (MRHD). However, spina bifida was observed in rabbits at a dose 40 times the MRHD.

(b) (4)

### Clinical Considerations

CNS stimulant medications, such as <TRADENAME>, cause vasoconstriction and thereby decrease placental perfusion

(b) (4)

### Data

#### *Animal Data*

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m<sup>2</sup> basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the

MRHD on a mg/m<sup>2</sup> basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m<sup>2</sup> basis). (b) (4)

## 8.2 Lactation

### Risk Summary

Methylphenidate is present in human milk. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for <TRADENAME> and any potential adverse effects on the breastfed child from <TRADENAME> or from the underlying maternal condition.

## 8.4 Pediatric Use

The safety and effectiveness of <TRADENAME> have been established in pediatric patients ages 6 to 17 years. Use of <TRADENAME> in pediatric patients 6 to 12 years of age (b) (4)

### Long Term Suppression of Growth

Growth should be monitored during treatment with CNS stimulants, including <TRADENAME>. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions* (5.7)].

### Juvenile Animal Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m<sup>2</sup> basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

## 12.1 Mechanism of Action

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

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 5 times the maximum recommended human dose on a mg/m<sup>2</sup> basis.

#### Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was (b) (4)

#### Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day, approximately 8 fold the maximum recommended human dose on a mg/m<sup>2</sup> basis.

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/s/  
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IKRAM M ELAYAN  
11/04/2015

LINDA H FOSSOM  
11/04/2015

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 207960

**NDA Number: 207960**

**Applicant: Pfizer**

**Stamp Date: 2/4/2015**

**Drug Name: methylphenidate NDA Type: 505 (b)(2)**

**HCl Extended-Release**

**Chewable Tablets**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is a 505(b)(2) application in which Methylin Chewable Tablets (NDA 021475) is the reference listed drug. There were no non-clinical studies submitted and no chemistry issues that affect non-clinical were identified.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_207960

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 207960**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_Yes\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Ikram Elayan  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Linda Fossom  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

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/s/  
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IKRAM M ELAYAN  
03/27/2015

LINDA H FOSSOM  
03/27/2015