

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205831Orig1s000**

**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: 205831  
Supporting document/s: 000  
Applicant's letter date: 6/18/2014  
CDER stamp date: 6/18/2014  
Product: Methylphenidate HCl ER Capsules (Aptensio)  
Indication: Attention Deficit Hyperactivity Disorder (ADHD)  
Applicant: Rhodes Pharmaceuticals  
Review Division: Division of Psychiatry Products  
Reviewer: Ikram Elayan, Ph.D.  
Supervisor/Team Leader: Linda Fossom, Ph.D.  
Division Director: Mitchell Mathis, M.D. CPH  
Project Manager: ShinYe Chang, Pharm.D.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205831 are owned by Rhodes Pharmaceuticals or are data for which Rhodes Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 205831 that Rhodes Pharmaceuticals 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 205831

# 1 Executive Summary

## 1.1 Introduction

This is a 505(b)(2) application for methylphenidate HCl extended release capsules proposed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 (b)(4) of age. The reference drugs for this application are Ritalin and Ritalin LA.

## 1.2 Brief Discussion of Nonclinical Findings

No non-clinical studies were submitted with this application and none would be needed unless there were chemistry issues that would impact non-clinical.

The chemistry review team identified one degradation product (b)(4) that was specified at levels NMT (b)(4)%. However, the sponsor agreed to lower the specification levels of this enantiomer from NMT (b)(4)% to NMT (b)(4)% (qualification threshold for degradation products in new drug products), as stated in their letter dated 9/18/2014. Consequently there are no non-clinical issues.

In addition, the labeling for section 8.1 was updated to be consistent with the new Pregnancy and Lactation Labeling Rule (PLLR) approved December 4, 2014<sup>1</sup>.

## 1.3 Recommendations

### 1.3.1 Approvability

From a non-clinical point of view this application may be approved pending the labeling negotiations.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

The proposed labeling, including non-clinical information in section 8.1 based on the new PLLR, is being negotiated with the sponsor at this time. The final labeling will be included in the approval letter to the sponsor.

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<sup>1</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

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/s/  
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IKRAM M ELAYAN  
03/18/2015

LINDA H FOSSOM  
03/18/2015

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 205831

**NDA Number: 205831**

**Applicant: Rhodes  
Pharmaceuticals**

**Stamp Date: 6/18/2014**

**Drug Name: methylphenidate hydrochloride extended  
release capsule**      **NDA Type:505(b)(2)**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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		No nonclinical data were submitted. This is a 505(b)(2) NDA in which Ritalin LA and Ritalin are the reference drugs.
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		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 205831**

	<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		The (b)(4) was identified as one of the degradation products. It was specified at levels of NMT (b)(4)%. The sponsor will be asked to either lower the specification levels to NMT (b)(4)% or justify the levels proposed.
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?			N/A

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

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

The application is considered fileable.

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

The sponsor will be asked to either lower the specification levels for the (b)(4) in the drug product to NMT (b)(4)% or justify the specification level of NMT (b)(4)%.

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Reviewing Pharmacologist Date

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Team Leader/Supervisor Date

File name: Pharmacology\_Toxicology Filing Checklist for NDA205831

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/s/  
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IKRAM M ELAYAN  
08/18/2014

LINDA H FOSSOM  
08/18/2014