

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205831Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205831	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Aptensio XR Established/Proper Name: methylphenidate Dosage Form: extended-release capsule Strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, (b) (4)		
Applicant: Rhodes Pharmaceuticals, LP		
Date of Receipt: June 18, 2014		
PDUFA Goal Date: April 18, 2015	Action Goal Date (if different): April 17, 2015	
RPM: Shin-Ye Sandy Chang, Pharm.D.		
Proposed Indication(s): Attention Deficit Hyperactivity Disorder		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Ritalin (NDA 010187)	FDA's previous finding of safety and effectiveness: Nonclinical Toxicology

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

RP-BP-PK001: Bioavailability Study of a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule, a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule Dosed as Sprinkles vs. Reference 25 mg Ritalin® IR Given Three Times Daily in Healthy Adults under Fasted Conditions

RP-BP-PK002: Steady State Comparative Bioavailability Study of Biphentin™ Methylphenidate Hydrochloride ER Capsule 80 mg vs. Reference Ritalin® IR 25 mg Three Times Daily in Healthy Adults Under Fed Conditions

RP-PopPK001: Population Pharmacokinetic Modeling of Biphentin™ Methylphenidate Hydrochloride Capsules

RP-PopPK002: Population Pharmacokinetic/Pharmacodynamic Modeling of Biphentin™ Methylphenidate Hydrochloride Capsules in Pediatric Patients

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “**NO**”, proceed to question #5.
 If “**YES**”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
 If “**NO**,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Ritalin	01078	Y
Ritalin LA	21284	Y <i>(DPP believes that the applicant erroneously specified reliance on Ritalin LA)</i>

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO
 If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “**N/A**”.
 If “**NO**”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:
 a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form. The ratio of immediate-release content to controlled-release content (approximately 40% / 60%) in the formulation is unique among the available controlled release methylphenidate products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):
NDA 21259 Metadate CD (generic available)
NDA 21284 Ritalin LA (generic available)

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

NDA	Name	Dosage Form	Generic
202100	Quillivant XR	Powder for extended-release suspension	No
21121	Concerta	Extended-release tablets	Yes
21514	Daytrana	Transdermal patches	No
21475	Methylin	Chewable tablets	No

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
 Patent number(s): N/A
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
 Patent number(s): _____ Expiry date(s): _____
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
 Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

SHIN-YE CHANG
04/17/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 30, 2015

To: Sandy Chang, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 205831**
APTENSIO XR™ (methylphenidate hydrochloride) Extended-Release Capsules,
CII

OPDP has reviewed the draft product labeling (PI) and Medication Guide (MG) for APTENSIO XR™ (methylphenidate hydrochloride) Extended-Release Capsules, CII (Aptensio XR) requested in the consult from DPP dated August 26, 2014.

OPDP's comments on the draft PI for Aptensio XR are based on the version provided by Sandy Chang via email to Aman Sarai in the Division of Medical Policy Programs (DMPP) on March 20, 2015. Combined OPDP and DMPP comments on the proposed MG were provided to DPP on March 27, 2015.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SUSANNAH O'DONNELL
03/30/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Medical Team Leader
DPMH
Lynne P. Yao, MD, Acting Division Director
DPMH

NDA Number: 205,831

Sponsor: Rhodes Pharma

Indication: Attention Deficit/Hyperactivity Disorder (ADHD)

Drug, Route of Administration Aptensio XR (methylphenidate), capsules for oral administration

Dosing regimen: To be determined (TBD); starting dose 10 mg/day (qD)

Proposed Pediatric Regimen: TBD

Division Consult Request: The Division of Psychiatry Drug Products (DPP) requests assistance with labeling for sections 8.1, 8.3, and 8.4 of proposed labeling to ensure conformity with the Pregnancy Rule.

Background

Aptensio XR (methylphenidate hydrochloride) extended release capsules is a stimulant medication under development for treatment of patients with attention deficit/hyperactivity disorder (ADHD) in affected patients 6 years and older.

A brief overview of ADHD and approved drug treatments is provided below, followed by a brief summary of the phase 3 studies performed to support labeling, and the labeling review.

Disease Background

ADHD is defined by the diagnostic and statistical manual 5th edition (DSM5) of the American Psychiatric Association as a persistent pattern or inattention and/or hyperactivity-impulsivity that interferes with functioning or development.¹

While prevalence figures in the United States population vary, data suggest that ADHD occurs in 3 to 10% of school aged children, 10 to 60% of whom have symptoms as adults (up to 4% of the adult population).^{2,3,4}

Treatment includes a combination of behavioral therapy and drug therapy. Approved drug therapies fall into two broad categories: non-stimulant medications (e.g., clonidine, [NDA 22,331] and guanfacine [NDA 22,037]), for patients 6 years and older; atomoxetine [NDA 21,411] for patients 6 years and older) and stimulant medications (methylphenidate- and amphetamine-like products). Most stimulant medications for ADHD treatment are approved for use in patients 6 years and older; however, several products such as Adderall ANDA (ANDA 40422) and two dextroamphetamine ANDAs (ANDA 203644 and ANDA 84051) are approved for patients 3 years and older.

Clinical program

The sponsor conducted two safety and efficacy studies in affected pediatric patients, 6 to 18 years old, to support labeling.

Protocol RP-BP-EF001 was a Phase 3, randomized, double-blind study of the time course of response of MPH-MLR capsules compared to placebo in 27 (20 for efficacy) children 6 to 12 years of age with ADHD in an analog classroom setting.

Protocol RP-BP-EF002 was a multi-center Phase 3, randomized, parallel, double-blind efficacy and safety study of MPH-MLR capsules compared to placebo in 225 (221 for efficacy) children and adolescents 6 to 18 years with ADHD.

At the February 9, 2015, internal labeling meeting, DPP stated that the studies appeared to be appropriately designed and executed to assess efficacy and short-term safety. The sponsor intends to request partial waiver for neonates and other children younger than (b)
(4)

¹ American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

² Wilens T, Faraone S, Biederman J, Attention-deficit/hyperactivity disorder in adults. JAMA. 2004 Aug 4;292(5):619-23.

³ Kessler R, Adler L, Barkley R., et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006; 163(4):716-723.

⁴ Gentile J, Atig R, Gillig P. Adult ADHD Diagnosis, Differential Diagnosis, and Medication Management. Psychiatric (Edgemont). Aug 2006;3(8):25-30.

years based on the rationale that the product would be (b) (4) for which the waiver is requested.

Reviewer comment: The Agency has recently determined that development of stimulant drugs to treat ADHD may be appropriate in children 4 years and older and at least one Written Request (WR) has been issued (b) (4). Therefore, DPMH recommends a partial waiver of studies in patients younger than 4 years. Studies in children ages 4 and 5 years should be deferred requirements under PREA and potentially requested through issuance of a WR.

Labeling Review

This labeling review is based on the labeling version located in SharePoint on February 3, 2015. The Pediatric labeling review is limited to review of the proposed Boxed Warning, sections 1 (Indications and Usage), 2 (Dosage and Administration), 4 (Contraindications), 5 (Warnings and Precautions), and section 8.4 (Pediatric Usage). Sections 8.1 and 8.3 will be addressed in the separate Maternal Health labeling consult. The current draft versions of sections 6 and 14 are provided below.

For each section, the suggested labeling is presented first and is followed by suggested revisions which are noted in ***bold italics***.

Boxed Warning

Proposed

CNS stimulants, including APTENSIO XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see Warning and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].

Reviewer comments: This boxed warning matches the boxed warning for other stimulant medications intended for treatment of ADHD (e.g., Adderall XR, NDA 21,303) and is appropriate.

1 Indications and Usage

Proposed

APTENSIO XR is (b) (4) indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Reviewer comments: The proposed indication is acceptable. DPMH has previously expressed the opinion that the age for which drugs are indicated should be stated in indication statements, but acknowledges the possibility that such statements may unintentionally restrict use. Additionally, the draft labeling included the following statement in the Highlights section, USE IN SPECIFIC POPULATIONS:

(b) (4)
(b) (4)

2 Dosage and Administration

Proposed



APTENSIO XR may be taken whole, or the capsule may be opened and the entire contents sprinkled onto (b) (4) applesauce. If the patient is using the sprinkled administration method, the sprinkled (b) (4) should be consumed immediately; it should not be stored. Patients should take the (b) (4) with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

(b) (4)

(b) (4)

Reviewer comment: At the internal meeting of February 9, 2015, DPP and Clinical Pharmacology stated that this section was undergoing revision. At that meeting DPP and Clinical Pharmacology agreed that the current paragraph describing the starting dose (b) (4) and dose titration. The labeling revision in SharePoint on February 17, 2015, has been revised as shown below and appears appropriate.

“The recommended starting dose of APTENSIO XR for patients 6 years and above is 10 mg once daily in the morning with or without food. The dose should be individualized according to the needs and response of the patient.

The dose may be titrated weekly in increments of 10 mg, after [REDACTED] (b) (4) 7 days between dosage increases. Daily dosages above 60 mg have not been studied and are not recommended.”

4 Contraindications

The following list of contraindications is current as of February 17, 2015; however, DPP has requested formatting revisions to the Contraindications section of labeling in order for the labeling to be conformance with current labeling guidance.

Proposed

Hypersensitivity to methylphenidate or other components of the product [see Adverse Reactions (6.1)].

Concomitant treatment with monoamine oxidase inhibitors, and also within [REDACTED] (b) (4) (b) (4) 14 days following discontinuation of treatment with a monoamine oxidase inhibitor [REDACTED] (b) (4) [see Drug Interactions (7.1)].

Reviewer comment: The above contraindications were discussed with DPP at the labeling meeting on February 9, 2015. DPP stated that while labeling for stimulant medications is growing into greater class conformity, some differences still exist. The draft labeling from February 9, 2015, contained additional contraindications for [REDACTED] (b) (4). Based on discussions with DPP at the February 9, 2015, meeting and current labeling guidance which discourages listing theoretical risks [REDACTED] (b) (4) in Contraindications, DPP has removed these terms from Contraindications.

5 Warnings and Precautions

5.1 Potential for Abuse and Dependence

Proposed

CNS stimulants, including APTENSIO XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see Drug Abuse and Dependence (9.2, 9.3)].

Reviewer comment: This language is acceptable and is consistent with other stimulant medications for treatment of ADHD and the Boxed Warning as noted earlier in this document.

5.2 Serious Cardiovascular Events

Proposed

Sudden Death [REDACTED] (b) (4)

[REDACTED] (b) (4)

Sudden death has been reported in (b) (4) with CNS stimulant treatment at (b) (4). Avoid use in (b) (4) with known (b) (4) structural cardiac abnormalities, cardiomyopathy, serious heart (b) (4) other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during (b) (4) APTENSIO XR.

Reviewer comment: This language is acceptable and is consistent with other stimulant medications for treatment of ADHD (Adderall XR). Other stimulant medications also describe risk for adults. (b) (4)

5.3 Blood Pressure and Heart Rate Increases

(b) (4)

Reviewer comment: This language is acceptable and is consistent with other stimulant medications for treatment of ADHD (Adderall XR).

5.4 Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/ manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

(b) (4) New Psychotic or Manic Symptoms

(b) (4) psychotic or manic symptoms, e. g., hallucinations, delusional thinking, or mania in (b) (4) without a prior history of psychotic illness or mania (b) (4). If such symptoms occur, consider discontinuing APTENSIO XR. In a pooled analysis of multiple short-term, placebo-controlled studies, (b) (4) symptoms occurred in (b) (4) 0.1% (b) (4).

(b) (4) of
stimulant-treated patients compared to 0 in placebo-treated patients.

Reviewer comment: This language is acceptable and is consistent with other stimulant medications for treatment of ADHD (e.g., Adderall XR).

5.5 Long-Term Suppression of Growth

(b) (4)
Careful follow-up of weight and height in (b) (4) ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated (b) (4) (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well.

Reviewer comment: This language is generally acceptable and is consistent with other stimulant medications for treatment of ADHD (e.g., Adderall XR). DPMH notes that the term “naturalistic” is unclear and recommends clarification.

(b) (4)

5.9 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug

withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Reviewer comment: The above language is consistent with recent labeling for other stimulant medications indicated for treatment of ADHD (e.g., Focalin, NDA 21,278 and Strattera, NDA 21,411). To date, no priapism events have been reported in clinical studies of Aptensio.

5.10 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Reviewer comment: This language is generally acceptable and is consistent with other stimulant medications for treatment of ADHD (e.g., Focalin, NDA 21,278).

6 Adverse Reactions

At the time of this review, the Adverse Reactions section was undergoing substantial revision, which limits DPMH's ability provide informative comments.

Proposed

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported ($\geq 2\%$ of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: decreased appetite, decreased weight, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

Clinical Trials Experience with APTENSIO XR in (b) (4) with ADHD

Two APTENSIO XR clinical studies evaluated a total of 256 patients with ADHD. Two hundred and forty-three (243) patients participated in the double-blind phase of these two

clinical studies (b) (4)

Study 1 (b) (4) was a randomized, double-blind, single center, placebo-controlled (b) (4) study to evaluate the time of onset, duration of efficacy, tolerability and safety (b) (4) 15 mg, 20 mg, 30 mg or 40 mg of (b) (4) in 26 pediatric (b) (4) patients aged 6 to 12 years who met DSM-IV criteria for ADHD (b) (4) [See Clinical Studies (14)].

Most Common Adverse Reactions (incidence of $\geq 5\%$ and at a rate at least twice placebo): abdominal pain, pyrexia and headache.

Study 2 (b) (4) was a (b) (4) randomized, double-blind, multicenter, placebo-controlled, (b) (4) dose study of 10 mg, 15 mg, 20 mg, (b) (4) 40 mg, (b) (4) of APTENSIO XR in 221 (b) (4) (6 to 17 years of age) who met DSM-IV criteria for ADHD (b) (4) [See Clinical Studies (14)].

Most Common Adverse Reactions (incidence of $\geq 5\%$ and at a rate of at least twice placebo): abdominal pain, decreased appetite, headache and insomnia.

Adverse Events Leading to Discontinuation (b) (4)

Table 2: Common Adverse Reactions Occurring in $\geq 2\%$ (b) (4) (Ages 6 to 17 years) in Study 2.

(b) (4)

(b) (4)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Reviewer comment: The adverse reaction list in for the above paragraph has not been received. DPP requested that the sponsor include the postmarketing adverse reactions language from approved methylphenidate labeling (pending). As noted above, seizures and visual disturbances will be described in Postmarketing Experience.

8.4 Pediatric Use

Proposed

(b) (4)

The safety and effectiveness of APTENSIO XR have been established in pediatric patients ages 6 to 17 years. (b) (4) adequate and well-controlled (b) (4) [see Clinical Studies (14)]. (b) (4)

The long-term efficacy of methylphenidate in pediatric patients has not been established. (b) (4)

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including APTENSIO XR. (b) (4) who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.4)].

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/m² 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/m² 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/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Reviewer comment: The preceding language is generally appropriate; however DPMH recommends the following changes to enhance readability.

The safety and effectiveness of APTENSIO XR in children under six years have not been established.

The safety and effectiveness of APTENSIO XR have been established in pediatric patients ages 6 to 17 years. Use of APTENSIO XR in pediatric patients 6 to 12 years of age is supported **by two** adequate and well-controlled clinical trials [see *Clinical Studies (14)*]. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of APTENSIO XR in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including APTENSIO XR. **Pediatric patients** who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.4)*].

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/m² 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/m² 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/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

14 Clinical Studies

Reviewer comment: This section is still undergoing substantial revisions by DPP which precludes informed review and comment. DPMH reviewed the section in advance of the February 9, 2015, labeling meeting and our one comment was to recommend the use of the term 'pediatric patients' for the entire study group rather than using the phrase (b) (4) patients.

Conclusions and Recommendations

DPMH participated in the internal labeling meetings (February 9 and 23, 2015) and provided the above comments and recommendations to DPP in advance of the internal meetings. The final negotiated labeling (pending) may contain additional revisions not discussed in this document, particularly for the Adverse Reactions and Clinical Studies sections of labeling.

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

/s/

ETHAN D HAUSMAN
03/23/2015

HARI C SACHS
03/23/2015
I agree with these recommendations.

LYNNE P YAO
03/27/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 27, 2015

To: Mitchell Mathis, M.D.
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): APTENSIO XR (methylphenidate hydrochloride)

Dosage Form and Route: Extended Release Capsules, for oral use

Application Type/Number: 205831

Applicant: Rhodes Pharmaceuticals, LP

1 INTRODUCTION

On June 18, 2014, Rhodes Pharmaceuticals LP submitted for the Agency's review a Original New Drug Application seeking approval to market Aptensio XR Capsules. APTENSIO XR is a Central Nervous System(CNS) stimulant with a proposed indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on August 27, 2014, and August 26, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for APTENSIO XR (methylphenidate hydrochloride) extended-release capsules, for oral use.

2 MATERIAL REVIEWED

- Draft APTENSIO XR (methylphenidate hydrochloride) MG received on June 18, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2015.
- Draft APTENSIO XR (methylphenidate hydrochloride) Prescribing Information (PI) received on June 18, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2015.
- Approved Quillivant XR (methylphenidate hydrochloride) comparator labeling dated December 12, 2013.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

AMANPREET K SARAI
03/27/2015

SUSANNAH O'DONNELL
03/27/2015

MELISSA I HULETT
03/27/2015

LASHAWN M GRIFFITHS
03/27/2015



Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: March 13, 2015 **Date consulted:** December 16, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products (DPP)

Drug: Aptensio XR (methylphenidate hydrochloride extended release) capsules

NDA: 205831

Applicant: Rhodes Pharmaceuticals

Subject: Pregnancy and Nursing Mothers Labeling

Materials

Reviewed:

- DPMH consult request dated December 16, 2014, DARRTS Reference ID 3674409
- Sponsor's submitted background package for NDA 205831, Aptensio XR
- DPMH consult review of Quillivant (methylphenidate HCl) Extended-Release Powder for Oral Suspension-NDA 202100, September 20, 2012, DARRTS Reference ID 3192069.
- Pregnancy and Nursing Mothers subsections of methylphenidate labeling

Consult Question:

DPP requests DPMH to "review labeling to ensure that it conforms to the Pregnancy Rule, i.e., sections 8.1, 8.3, and 8.4 of the PI."

REGULATORY HISTORY

Aptensio XR (methylphenidate hydrochloride extended-release) is central nervous system (CNS) stimulant. On June 18, 2014, Rhodes Pharmaceuticals submitted a 505 (b)(2) New Drug Application (NDA 205831) for Aptensio XR (methylphenidate) to obtain approval to market Aptensio XR for the proposed indication of the treatment of patients with Attention-Deficit Hyperactivity Disorder (ADHD) in patients 6 years old and older.

The Division of Psychiatry Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 16, 2014, to provide input for appropriate labeling of the pregnancy and lactation subsections of Aptensio XR labeling to comply with Pregnancy and Lactation Labeling Rule format.

BACKGROUND

ADHD and Pregnancy

ADHD affects 4.4% of adults in the United States and is associated with an elevated risk of poorer general and mental health, substance abuse, impaired work performance. There have been no studies evaluating the course of ADHD in pregnancy and the postpartum period. While many women with ADHD can stop their medications during pregnancy without adverse effects, for other women, functional impairment may be severe. Some women with ADHD may be at an increased risk of motor vehicle accidents and have severe impairments in occupational, school and work functioning.¹

It is estimated that 30% of patients continue ADHD medications into adulthood. In an ongoing case-control surveillance study, Slone Epidemiology Center's Birth Defects Study (BDS), the prevalence of ADHD medication use was analyzed. In this study, 29,540 women were interviewed between 1998 and 2014, and there were 87 reported exposures to an ADHD medication. Although the overall prevalence of use of any ADHD medication was 0.3%, there was a marked increase in the prevalence of use over the period of the study, from 0.2% for women with last menstrual period (LMP) dates in 1997-1998 to 1.3% for women with LMP dates in 2013. The most commonly reported ADHD medication was amphetamine mixed salts (57.5%), followed by methylphenidate (29.9%). Of the 87 women who were exposed to an ADHD medication, all but one used it during the first trimester; 18 continued use into the second trimester, and 11 continued use into the third trimester. In a recent letter to the editor, Louik *et al.*, noted that although the use of ADHD medications in pregnancy is increasing, there is lack of information regarding potential fetal risks in humans and a need for post-marketing studies.²

Methylphenidate and Drug Characteristics

Methylphenidate hydrochloride is a CNS stimulant indicated for the treatment of ADHD in adults and children. Common adverse events seen in children and adults who take methylphenidate include: decreased appetite, weight loss, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation,

¹ Freeman, MP. ADHD and pregnancy. *Am J Psychiatry*. 2014; 171 (7): 723-8.

² Louik et al. Increasing use of ADHD medications in pregnancy. *Pharmacoepidemiology and Drug Safety*. 2015; 24: 218-220.

irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

Methylphenidate hydrochloride is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of monoamines into the extraneuronal space. Methylphenidate has the following characteristics:

- Molecular weight: 269.77
- pH 8.77
- Half-life: 5.09-5.43 hrs.
- Protein Binding: 10-33%
- Oral Bioavailability: [REDACTED]

(b) (4)

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁴ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁵ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Experience

The applicant did not perform additional nonclinical studies for methylphenidate and relied on information from the reference listed drug Quillivant XR (methylphenidate) to satisfy nonclinical requirements.

Overall, the pharmacology/toxicology reviewer noted that oral administration of methylphenidate to pregnant rabbits and rats during organogenesis was associated with an increased incidence of fetal spina bifida in rabbits at a dose 40 times the maximum recommended human dose (MRHD) and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD. A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD.

Reviewer Comments:

In general, when animal doses are expressed as multiples of a human dose, an animal dose that is less than or equal to 10 times the MRHD, is concerning for causing similar adverse

³ <http://www.drugbank.ca/drugs/db00422>. Accessed 2/16/2015

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

⁵ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

events in humans. When the adverse event involves a less severe adverse event, such as decrease in body weight gain, an animal dose less than five times the MRHD would be significant for seeing similar findings in humans. However, in the information noted above, skeletal variations in rats, which occurred at seven times the MRHD, were associated with maternal toxicity, and this is not a relevant safety finding for humans.

When the animal dose is greater than 15 times the MRHD, then the risk of that adverse event is less likely in humans. However, when the adverse event involves a condition, such as spina bifida in rabbits noted in the discussion above, which is a rare event in both humans and animals, then this finding is relevant and should be included in labeling.

Methylphenidate and Pregnancy

The sponsor did not conduct studies with Aptensio XR in pregnant women. A search of published literature in Pubmed was performed to review published data regarding methylphenidate in pregnancy. Limited published studies were found.

Pottegard, et al. (2014)

A prospective cohort study (Pottegard, et al.) used data from four Danish Registries: the Danish National Patient Register, the Danish National Prescription Registry, the Danish Medical Birth Registry, and the Danish Civil Registration System. Data for the period of January 1, 1995 to December 31, 2012. To be included in the cohort of pregnancies exposed to methylphenidate in the first trimester, the mother was required to have picked up one or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. The unexposed cohort included pregnancies in which the mother had not redeemed a prescription for a psychostimulant at any time point prior to the end of the pregnancy. Of the 460,323 pregnancies resulting in live births, 222 pregnancies were exposed to methylphenidate during the time period and were matched with 2,220 unexposed subjects. Among the exposed patients, there were seven major malformations (3.2%), and of these, three (1.4%) were cardiac malformations. These rates were comparable to those in the unexposed group who had a rate of 3.9% for major malformations and 1.4% for cardiac malformations.⁶

Reviewer Comments:

The study reviewed above only included 222 pregnancies exposed to methylphenidate compared to 2,200 unexposed pregnancies. There were not enough methylphenidate exposed pregnancies to allow risk estimates of specific malformations. The estimate of cardiac malformations is limited by the sample size and outcome frequency. Although the results of the cardiac malformations are not statistically significant, there were only three cardiac malformations observed and not enough statistical power for an appropriate analysis.

Also, there is no information on whether the pregnant women who picked up their methylphenidate prescriptions during the first trimester actually took the medication.

⁶ Pottegard, et al. First-Trimester Exposure to Methylphenidate: A Population-Based Cohort Study. The Journal of Clinical Psychiatry. 2014; 75(1): e88-e93.

Debooy, et al. (1993)

In retrospective chart review, Debooy *et al.*, identified 38 women who used intravenous pentazocine and methylphenidate during pregnancy. In addition to using pentazocine and methylphenidate, 27 women used alcohol and 10 women used other substances (marijuana (n=7), cocaine (n=2), diazepam (n=1)). All 38 women smoked cigarettes. Among 39 infants (including one set of twins) exposed *in utero* the following results were noted:

- 8 infants (21%) were delivered prematurely (less than 37 weeks at birth)
- 12 infants (31%) were small for gestational age (weight less than tenth percentile)
- 11 infants (28%) had withdrawal symptoms, including one infant noted to have seizures due to drug withdrawal
- 4 infants (10%) had congenital anomalies including one infant with a ventricular septal defect, one with polydactyly, and the set of twins both diagnosed with fetal alcohol syndrome.

The authors had follow-up developmental data from 30 infants. Of these, 22 infants had formal evaluations, and 18% of the formally evaluated infants had below normal scores.⁷

Reviewer Comments:

The study by Debooy, et al., was confounded by several factors, including the lack of a control group and the concomitant exposure from multiple substances that occurred in the majority of the pregnancies. In addition, the mother's social circumstances may have adversely affected the infant's development.

Dideriksen et al. (2013)

In a review of literature, Dideriksen *et al.*, reported on four cohorts that described birth outcomes after *in utero* exposure to methylphenidate. Out of the 180 first trimester exposures to methylphenidate, there were four major cardiac malformations seen. See the table below for details of these cohorts.⁸

Country	Source	Years	No of 1 st trimester exposed	# of malformations seen	Type of malformations
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⁷ Debooy VD, Seshia MM, Tenenbein M, et al. Intravenous pentazocine and methylphenidate abuse during pregnancy: Maternal lifestyle and infant outcome. American Journal of Diseases of Children. 1993;147(10):1062-65.

⁸ Dideriksen, et al. First Trimester In Utero Exposure to Methylphenidate. Basic and Clinical Pharmacology & Toxicology. 2013; 112 (2): 73-76.

The National Collaborative Perinatal Project (1977)

The National Collaborative Perinatal Project (CPP) of the National Institute of Neurological and Communicative Disorders and Stroke was a prospective study that ran from 1959 to 1974 and whose goal was to understand childhood neurologic disorders and other conditions. The CPP collected information on 50,282 women with medication exposure during pregnancy; mothers were examined during pregnancy, labor and delivery, and infants were given neonatal exams and followed-up at four, eight and twelve months, and three, four, seven and eight years old. The study reported on 367 women taking dextroamphetamine, 215 women taking unspecified amphetamines, and 11 women taking methylphenidate. All of these women had drug exposure in the first trimester. The methylphenidate exposure was analyzed as part of 96 pregnancies exposed to “other sympathomimetics,” which included 16 different drugs. No significant malformations were observed for the methylphenidate group. There were seven children with malformations in the “other sympathomimetics” group with a crude relative risk of 1.13 (95% CI not provided). There was no information on the specific nature of the malformations or to which of the specific medications these seven children had been exposed.⁹

Reviewer Comments

The data are difficult to interpret because the methylphenidate exposed patients comprised a small portion (11 of 96 total patients) and a separate analysis of these patients was not performed. Overall, there was no evidence of increased risk of malformations noted with methylphenidate and other sympathomimetics reviewed in the National Collaborative Perinatal Project.

Israeli Teratology Information Services (2011)

In a prospective comparative cohort study, Wajnbert, *et al.*, collected information from callers who contacted the Israeli teratology information service (TIS) between 2005 and 2009 regarding methylphenidate exposure. Fifty-four pregnancies were exposed to methylphenidate during pregnancies and of these, 52 were exposed in the first trimester. These pregnancies were compared to 54 pregnant women who contacted the TIS in regard to exposure to drugs that were not known to be teratogenic and matched by maternal age, gestational age at initial contact, and year. There were no congenital abnormalities noted in the methylphenidate first trimester exposed group. There were no significant differences in the rate of live-births or miscarriages between both groups. The average gestational age was 39 weeks in both groups. The birth weight was 3293 grams in the methylphenidate group versus 3300 grams in the control group ($p=0.879$).¹⁰

National Toxicology Program Center for Evaluation of Risks to Human Reproduction (2005)

The National Toxicology Program (NTP) established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)¹¹ in 1998. In January 2005, the NTP-CERHR

⁹ Heinonen OP *et al.* Birth Defects and Drugs in Pregnancy. Littleton Publishing Sciences Group. 1977. p8-15,345-355.

¹⁰ Wajnberg, *et al.* Pregnancy outcome after in-utero exposure to methylphenidate: A prospective comparative cohort study. *Reproductive Toxicology*. 2011; 21: 255-268.

¹¹ The CERHR is a publically accessible resource for information about adverse reproductive and/or developmental health effects associated with exposure to environmental and/or occupational chemicals. The

Amphetamine and Methylphenidate expert panel reviewed the article by Debooy, *et al.*, as well as data from the National Collaborative Perinatal Project discussed above. Overall, the expert panel determined that there was insufficient data to draw conclusions on an association between methylphenidate therapy in pregnant women and pregnancy loss and possible reproductive effects of methylphenidate in humans. Although there were studies investigating the effects of methylphenidate on human development, the studies were limited by inadequate study design and lack of appropriate controls. The NTP review panel noted that the data were insufficient to draw conclusions as to whether or not methylphenidate use by pregnant women is associated with pregnancy loss or other effects on the developing fetus.¹²

Reviewer Comments

There are limited data on the use of methylphenidate in pregnancy. The study by Pottegard reported on 222 pregnancies exposed to methylphenidate and noted a fetal malformation rate of 3.2%, which was comparable to the rates of fetal malformations in the unexposed group. However, there were not enough methylphenidate exposed pregnancies to allow risk estimates of specific malformations.

The meta-analysis by Dideriksen, et al., reported on a total of 180 methylphenidate exposures during pregnancy with four cardiac malformations noted. However, it is difficult to draw a conclusion from these reports because the number of exposed pregnancies was small relative to the hundreds of exposures necessary to detect major fetal malformations.

Studies in animals have shown that prenatal and postnatal exposure to methylphenidate produces small litter size and low birth weight. Since low birth weight occurred in the offspring of rats at doses that were four times the MRHD, it is possible that this adverse event may be seen in humans. (See Nonclinical Experience: Reviewer Comments for details) The study by Debooy, et al., also suggested that methylphenidate may cause low birth weight and, in addition, may result in shortened gestation and infant withdrawal. However, the study by Debooy, et al., did not have a control group and was confounded by maternal use of multiple drugs.

Methylphenidate and Lactation

The Drugs and Lactation Database (LactMed)¹³ and Pubmed were searched for available lactation data on the use of methylphenidate, and limited evidence indicates that methylphenidate levels in breast milk are low, and there is no evidence of adverse effects on

CERHR convenes a scientific expert panel that meets in a public forum to review, discuss and evaluate scientific literature on a selected chemical.

¹² NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Methylphenidate, March 2005. <http://ntp.niehs.nih.gov/ntp/ohat/stimulants/methylphenidate/methylphenidatemonograph.pdf>

¹³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

nursing infants. The effects of methylphenidate in milk on the neurological development of the infant have not been well studied.

Hackett, et al. (2006)

In a case report by Hackett, *et al.*, a 26-year old, six months postpartum, lactating female with ADHD was evaluated. The patient was taking methylphenidate 40mg twice daily, 5 days/week for 5.5 weeks prior to testing, but took methylphenidate for 7 consecutive days immediately before blood and milk samples. The subject had samples of breast milk collected before her first morning dose of methylphenidate and at each of the seven times her 6-month old infant breast-fed over the following 24 hours. Infant blood samples were taken before the first morning dose and at 2.2, 4, 6.2 and 24 hours thereafter. The average milk level of methylphenidate over the 24 hours after the dose was 15.4 mcg/L. The authors calculated that the infant would receive 2.3 mcg/kg daily or 0.2% of the maternal weight-adjusted dose. The mother reported the infant to be sleeping, eating, and gaining weight normally.¹⁴

Hackett, et al. (2005)

In a lactation study by Hackett, *et al.*, three mothers, an average of four months postpartum with an average age of 33, taking an average of 52 mg (range 35-80 mg/day) of methylphenidate daily for ADHD, were studied. Milk and blood samples were obtained from the mothers and blood samples were taken from the infants (average age 4.4 months). The mean milk/plasma ratio was 2.7. The methylphenidate concentration in milk was 19 mcg/L, which resulted in an infant dose of 2.9 mcg/kg/day or 0.7 % of the maternal weight-adjusted dosage, which was calculated by the authors. The infants were assessed by the study team and showed normal progress for age and no drug-related adverse effects. There was no mention of how the infants were assessed.¹⁵

Spigset et al. (2007)

In another case report by Spigset *et al.*, a 31 year old lactating patient treated with methylphenidate for narcolepsy was breastfeeding an 11-month old infant. The patient took a total of 15 mg daily of methylphenidate immediate release tablets (5 mg in the am and 10 mg at noon). Maternal serum and breast milk were collected at five points of time during a 24 hours period (immediately before the morning dose at 8 AM, just before the noon dose and at 4, 8 and 21 hours after the noon dose). The first three samples of breast milk were from the foremilk,¹⁶ and the last two samples of breast milk were from the hindmilk¹⁷. The maternal serum concentrations in the five samples were <0.3, 2.3, 3.8, 1.7, and <0.3 ng/ml, respectively. The corresponding milk concentrations were <0.3, 2.4, 5.9, 1.4, and <0.3 ng/ml. Accordingly, in the three samples with measurable concentrations, the mean milk/serum concentration ratio 1.1. In this patient, the authors calculated the infant dose to be 0.38

¹⁴ Hackett LP, Kristensen JH, Hale TW, Paterson R, Ilett KF. Methylphenidate and breast-feeding. *Ann Pharmacother.* 2006; 40(10):1890-1

¹⁵ Hackett LP, Ilett KF, Kristensen JH et al. Infant dose and safety of breastfeeding for dexamphetamine and methylphenidate in mothers with attention deficit hyperactivity disorder. *Ther Drug Monit.* 2005; 27(2):220-1.

¹⁶ Foremilk: found at the beginning of a feeding session and contains more water, vitamins, and protein.

¹⁷ Hindmilk: occurs after the initial release of milk and contains higher levels of fat and helps in infant weight gain.

mcg/kg/day or 0.16% of the maternal weight based dose. The infant was sporadically breastfed and no adverse effects were observed by the mother.¹⁸

The American Academy of Pediatrics Committee on Drugs (2013)

The American Academy of Pediatrics Committee on Drugs 2013 reports that amphetamine exposure in the breastfeeding infant has resulted in cases of infant hypertension, tachycardia and seizures. In animal studies of postnatal exposure, long-term behavioral effects (learning and memory deficits), as well as altered locomotor activity, have been observed. Because current published data are insufficient to determine the long-term effects on infants exposed to stimulants through breast milk, physicians must counsel patients about the potential risks to an infant balanced with the risk of stopping the medication in the mother.¹⁹

Reviewer Comments

The characteristics of methylphenidate suggest that methylphenidate is present in breast milk. Methylphenidate has low protein-binding of 10-33% (medications with protein-binding less than 90% are more extensively excreted into breastmilk), a low molecular weight of 269.7 Daltons (drugs with molecular weights less than 800 Daltons are more readily transferred to the milk compartment), and a high pH of 8.77 (a higher pH means that more drug will be present in breast milk than in plasma).²⁰

In the case reports reviewed above, the milk/plasma (M/P) ratio ranged from 1.1 to 2.7. In general, a M/P ratio <1 indicates that the drug appears in breast milk in concentrations less than in plasma, a M/P ratio of 1 indicates that the drug levels in breast milk are similar to those in plasma, and a M/P >1 indicates that the drug is concentrated in breast milk. The M/P ratio calculation has limitations. M/P concentrations are often static measurements in time; however, milk composition and pH frequently change, even over the course of the same breastfeeding session, which causes the M/P concentration to change. Also, the way in which the M/P ratio is derived may affect the results. Many times the peak milk concentration is compared to the peak plasma concentration; however, these two concentrations were not taken at the same time, and this may provide an inaccurate M/P ratio.²¹ In addition, the M/P ratio of 2.7 may reflect an outlier and may not be representative of the usual findings. In order to determine a more accurate M/P ratio, more subjects would be needed in order to obtain a larger sample.

The relative infant dose (RID) was between 0.16% and 0.7% in the case reports reviewed above (a RID less than 10% of the maternal dose indicates that a medication is safe for breastfeeding), and there were no adverse effects noted in the infants studied. However, the amount of drug transferred into breast milk cannot be generalized to all nursing mothers. The infants in these case studies were older (4 months to 11 months) and were not fully reliant on breast milk as the primary source of nutrition. It is unknown if younger infants

¹⁸ Spigset O, Brede WR, Zahlén K. Excretion of Methylphenidate in Breast Milk. *Am J Psychiatry*. 2007. 164 (2); 348.

¹⁹ American Academy of Pediatrics: Committee on Drugs. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. *Pediatrics*. 2013; 132 (3): e796-809.

²⁰ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. *Journal of the American Pharmacists Association*. 2012; 51 (1): 86-94.

²¹ Black, Rebecca. *The Management of Breastfeeding*, Volume 4. 1998. Jones & Bartlett Learning.

who are only breastfed would have any adverse reactions. In addition, the composition of the breast milk and the levels of drug in breast milk may not reflect the levels in women who are breastfeeding younger infants.²²

Breastfeeding should not be contraindicated during maternal use of methylphenidate; methylphenidate exposure to a breastfeeding infant is likely low based on a RID less than 10%. Also, there have been no reported adverse events seen in infants of mothers who have taken methylphenidate while breastfeeding. If women chose to breastfeed while taking methylphenidate, they should be aware of potential side effects (agitation, insomnia, anorexia, and reduced weight gain) in their infants.²³

CONCLUSIONS AND RECOMMENDATIONS

Aptensio XR labeling is similar in content to Quillivant XR (methylphenidate hydrochloride) labeling, but has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with methylphenidate use in pregnant or lactating women. DPMH has the following recommendations for Aptensio XR labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of Aptensio XR labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” subsections²⁴.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of Aptensio XR labeling was formatted in the PLLR format to include: the “Risk Summary” and “Clinical Considerations” subsections²⁵.

DPMH APTENSIO XR (METHYLPHENIDATE HYDROCHLORIDE) LABELING

DPMH discussed our labeling recommendations with DPP at a labeling meeting on February 23, 2015. DPMH and the DPP Pharmacology/Toxicology team recommendations are below. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

²² Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

²³ Hale, Thomas. Medications and Mothers’ Milk: 15th edition. Hale Publishing, L.P. 2012

²⁴ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

²⁵ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published studies report on the use of methylphenidate in pregnant women; however, the data are insufficient to inform any drug-associated risks. No teratogenic effects were observed in an embryo-fetal development study 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 doses 40 times the MRHD. A decrease in pup body weight was observed in a pre-and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 4 times the MRHD [see Data]. The background risk of major birth defects and miscarriage for the indicated population are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal adverse reactions

CNS stimulants, such as APTENSIO XR, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

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/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m² 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/m² 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/m² basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m² basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m² basis).

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk

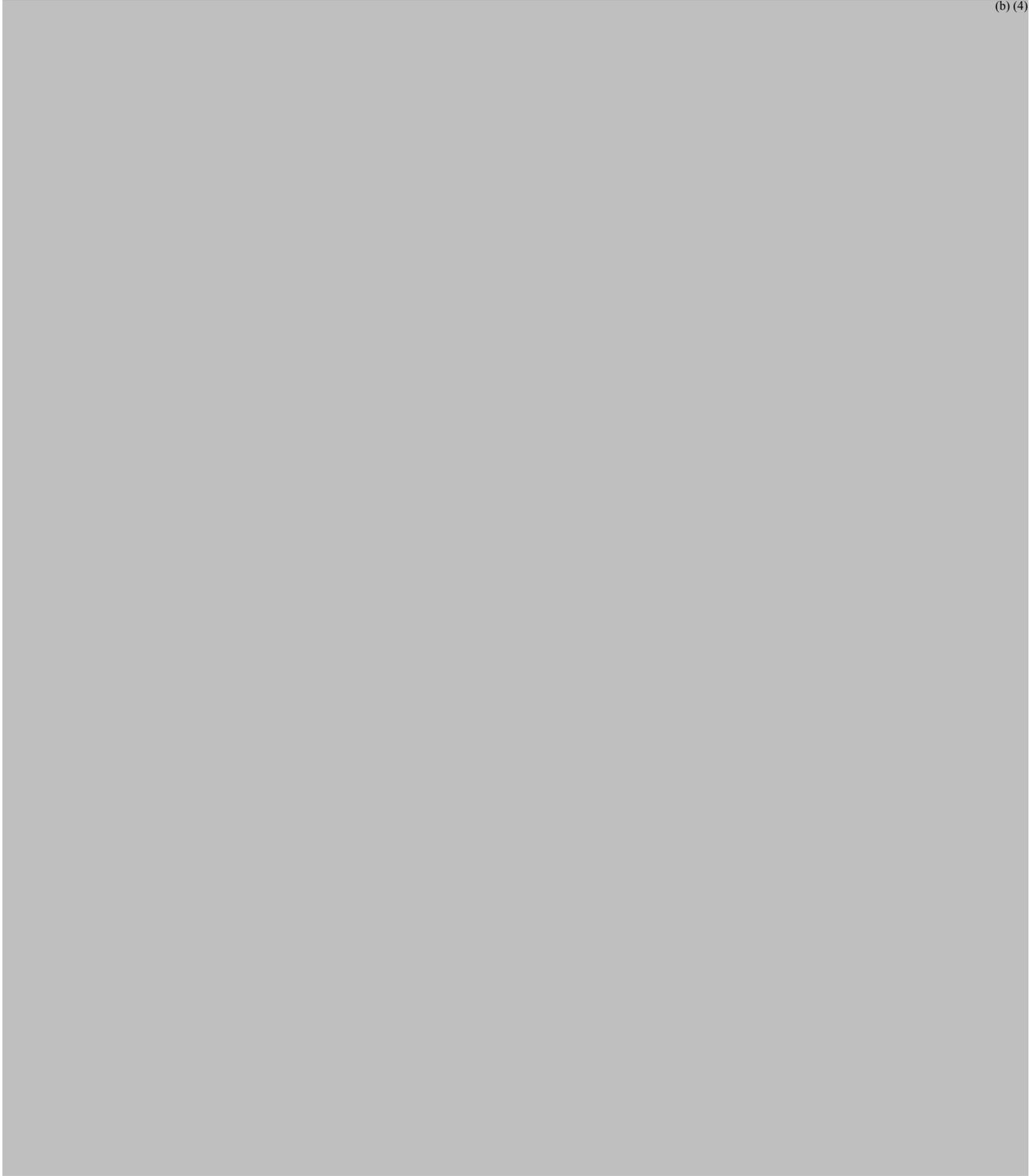
production. However, long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for APTENSIO XR and any potential adverse effects on the breastfed infant from APTENSIO XR or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

APPENDIX A – Applicant’s Proposed Aptensio XR Pregnancy and Nursing Mothers Labeling

(b) (4)



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

/s/

MIRIAM C DINATALE
03/13/2015

TAMARA N JOHNSON
03/13/2015

LYNNE P YAO
03/16/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 3, 2015

TO: Shin-Ye Chang, Pharm.D., Regulatory Project Manager
Cara Alfaro, Pharm.D., Clinical Analyst
Mark Ritter, M.D., Team Leader
Division of Psychiatry Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 205831

APPLICANT: Rhodes Pharmaceuticals, LP

DRUG: Methylphenidate extended release (Aptensio XR[®], proposed trade name)

NME: No

INDICATION: Treatment of attention deficit hyperactivity disorder (ADHD)

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: September 11, 2014

INSPECTION SUMMARY GOAL DATE: March 20, 2015

REGULATORY ACTION GOAL DATE: April 17, 2015

PDUFA DUE DATE: April 18, 2015

I. BACKGROUND

Rhodes Pharmaceuticals, L.C. (**Rhodes**) submitted this original NDA 205831 for Aptensio XR[®] (methylphenidate) for the treatment of attention deficit hyperactivity disorder (**ADHD**). This medication has been approved in Canada as Biphentin[®] since March 2006.

ADHD is a heterogeneous disorder characterized by persistently inappropriate inattentiveness, impulsivity, and/or hyperactivity, often with other comorbid psychiatric conditions. The pathogenesis of ADHD appears to involve neurotransmitter deficits; effective medications raise synaptic levels of norepinephrine, dopamine, and/or their precursors. Three subtypes of ADHD are recognized: hyperactive-impulsive, inattentive, and combined. ADHD is a common disorder with a prevalence of 5% worldwide in children and adolescents (age \leq 18 years).

Stimulants including methylphenidate and amphetamine are commonly used to manage ADHD. Although these medications are effective and have been available for decades, their side effects and abuse potential often limit their use. The particular delivery system is important to their pharmacokinetic (**PK**) profile, and pharmacodynamic (**PD**) effects (initial onset and duration of action) appear to be important to the overall efficacy, safety, treatment compliance, and patient quality of life. Aptensio XR[®] was designed as a daily single-dose alternative to multiple doses of immediate release methylphenidate. Rhodes claims that Aptensio XR[®] differs from other methylphenidate extended release formulations in that the PK and PD profiles more closely resemble those of immediate release formulations.

Rhodes sponsored Studies RP-BP-EF001 and RP-BP-EF002 in support of this NDA for the initial approval of Aptensio XR[®] (provisionally accepted trade name) in the United States (**US**). These two studies were audited at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites. In total, four specific study-sites were audited; both studies were audited at one of the three CI sites. The two studies are briefly described below with emphasis on study features relevant to inspectional findings. In these study descriptions, Aptensio XR[®] is referred to as Biphentin[®] (trade name approved in Canada).

Study RP-BP-EF001 (Study 001)

A Randomized, Double-Blind Study of the Time Course of Response to Biphentin[®] Methylphenidate Hydrochloride Extended-Release Capsules As Compared to Placebo in Children 6 to 12 Years with Attention Deficit Hyperactivity Disorder in an Analog Classroom Setting

This randomized, double-blind, placebo-controlled, cross-over study was conducted between January and June 2011 (six months) in 26 subjects at a single US site. The primary study objective was to evaluate the PD profile of Biphentin[®] relative to placebo over the first 12 hours after dosing (efficacy time course) in children (age 6-12 years) with ADHD. The study consisted of five phases: (1) screening and washout, up to four weeks; (2) open-label dose optimization, two to four weeks; (3) randomization and blinded cross-over, two weeks; (4) safety follow-up, one month; and (5) compassionate use, up to 21 months.

- Screening and washout: screening Visit 1, minimum two-day washout of any previous stimulant medication (at least five half-lives) prior to baseline Visit 2
- Open-label dose optimization: 15 mg/day initial Biphentin[®] dose at baseline Visit 2, upward titration to identify optimal dose (15, 20, 30, or 40 mg/day) to be maintained through blinded cross-over treatment
- Weekly dose adjustment: Visits 3-5, dose adjusted based on adverse events (**AEs**) and efficacy scores for ADHD Rating Scale, Fourth Version (**ADHD-RS-IV**) and Clinical Global Impression for Improvement (**CGI-I**).
- Randomization and blinded cross-over: (1) Visit 6, dispense optimized dose of initial study medication; (2) Visit 7, study evaluation then dispense alternate study medication; and (3) Visit 8, study evaluation
- Safety follow-up and compassionate use: phone call for AEs or concomitant medications since last visit; at CI discretion, continued treatment with monthly (early) to quarterly (late) follow-up

Major Inclusion Criteria

- Children (age 6-12 years) with ADHD (any subtype) per criteria specified in *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)* supported by Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime (**K-SADS-PL**)
- ADHD-RS-IV score \geq 90th percentile relative to the general population of children by age and gender and in need of pharmacological treatment for ADHD

Major Exclusion Criteria

- Current primary psychiatric diagnoses: severe anxiety disorder, conduct disorder, psychotic disorders, pervasive developmental disorder, eating disorder, obsessive-compulsive disorder, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder, or Tourette's syndrome (personal or family, per DSM-IV-TR and K-SADS-PL)
- Chronic medical illnesses including: seizure disorder (except febrile seizures), severe hypertension, untreated thyroid disease, known structural cardiac disorders, serious arrhythmias, cardiomyopathy, family history of sudden death, or glaucoma
- Use of monoamine oxidase inhibitors or any psychotropic medication with residual neurologic effect beyond 14 days from screening; any clinically significant electrocardiogram (**ECG**) or laboratory abnormalities at screening or baseline; Wechsler Abbreviated Scale of Intelligence (**WASI**) score $<$ 80

Treatment Groups and Regimen

- A single capsule of Biphentin[®] orally each morning during: (1) four weeks of open-label dose optimization, (2) one of two weeks of blinded cross-over treatment, and (3) any compassionate use
- Paired randomization (to force equal randomization ratio) to Biphentin[®] or placebo, one capsule orally each morning: randomized medication during first week and alternate medication during second week

Major Endpoints and Analyses

- Primary efficacy: mean score on Rating Scale by Swanson, Kotkin, Agler, M-Flynn, and Pelham (**SKAMP**) at nine pre-specified time points over 12 hours on evaluation Visits 7 and 8, comparison of scores for Biphentin[®] and placebo by mixed-effects analysis of covariance (**ANCOVA**)
- Time course of efficacy during blinded treatment, with efficacy measured using SKAMP at pre-specified times; SKAMP Department and Attention scores at each pre-specified time point
- Safety monitoring: AEs, Columbia Suicide Severity Rating Scale (**C-SSRS**), body weight, vital signs, ECG, laboratory testing, and concomitant medication use

Sponsor-Reported Outcome

- 26 subjects were enrolled, 22 were randomized, and 22 completed the study. Two subjects were excluded from analysis for: (1) receipt of placebo in both halves of cross-over treatment (medication packaging error), and (2) incomplete Visit 8 study evaluation (subject illness).
- Relative to placebo, lower SKAMP score for Biphentin[®] (least squares means): Biphentin[®] 1.3 and placebo 2.2 ($p = 0.0001$) with lower scores at each pre-specified time point ($p \leq 0.03$ for all time points) and efficacy at Hour 1 and sustained through Hour 12
- The study medication was well-tolerated with AEs limited to those known for other methylphenidate formulations commonly used for ADHD. No unexpected safety findings for methylphenidate treatment were observed, including results for laboratory tests, physical examination and vital signs, and ECG.

Study RP-BP-EF002 (Study 002)

A Randomized, Parallel, Double-Blind Efficacy and Safety Study of Biphentin[®] Methylphenidate Hydrochloride Extended Release Capsules Compared to Placebo in Children and Adolescents 6 to 18 Years with Attention Deficit Hyperactivity Disorder

This randomized, double-blind, placebo-controlled study was conducted between 2010 and 2013 in 230 subjects at 16 US sites. The primary study objective was to assess the efficacy of Biphentin[®] relative to placebo in the clinic setting using ADHD-RS-IV (clinician-administered parent version) in children and adolescents (age 6-18 years) with ADHD. Other than age, the subject selection criteria were identical to those for Study 001. The study consisted of five periods: (1) screening and washout, two days; (2) randomization and blinded treatment, one week; (3) open-label dose optimization, 11 weeks; (4) safety follow up, 30 days; and (5) optional compassionate use, up to 21 months.

- Screening and washout: screening Visit 1, minimum 48-hour washout of any previous stimulant medication if eligible for study
- Randomization and blinded treatment: (1) baseline Visit 2, randomization in equal ratio to four fixed-dose groups (Biphentin[®] 10, 15, 20, and 40 mg/day) or placebo for one week of blinded treatment, (2) Visit 3, study evaluations and study drug dispensed for open-label treatment
- Open-label dose optimization: continuation of treatment with Biphentin[®] (initial dose typically 10 mg; 15, 20, 30, 40, 50, or 60 mg also permitted per CI discretion), weekly dose titration at weekly Visits 4-7
- Safety follow-up, compassionate use: AEs and concomitant medication use since last visit (by phone); continued Biphentin[®] treatment with monthly (early) to quarterly (late) follow-up (CI discretion)

Major Endpoints and Analyses

- Primary: reduction from baseline (Visit 2) to the end of blinded treatment (Visit 3) in ADHD-RS-IV score, comparison of five groups (placebo and four Biphentin dose groups) by ANCOVA
- Secondary: comparison of Biphentin[®] dose levels and placebo for improvement from Visit 2 to Visit 3: (1) ADHD-RS-IV total and subscores (Hyperactivity-Impulsivity, Inattention), and (3) CGI-I
- Exploratory (for efficacy and/or safety): exploratory evaluation about sleep quality using Child's Sleep Habit Questionnaire (CSHQ), no impact intended on overall study outcome assessment
- Safety monitoring: AEs, C-SSRS, body weight, physical examination and vital signs, ECG, laboratory testing, and concomitant medication use

Sponsor-Reported Outcome

- 230 subjects were randomized, 221 completed blinded treatment, 200 completed open-label dose optimization, and 173 received compassionate Biphentin[®] treatment.
- After one week of blinded treatment, for Biphentin[®] relative to placebo, greater reduction was observed in: (1) ADHD-RS-IV total score (20 mg, $p = 0.01$; 40 mg, $p = 0.001$), (2) ADHD-RS-IV subscore for Hyperactivity-Impulsivity (40 mg, $p = 0.006$), (3) ADHD-RS-IV subscore for Inattention (20 mg, $p = 0.002$; 40 mg, $p = 0.003$), and (4) CGI-I (20 mg, $p = 0.03$; 40 mg, $p = 0.007$).
- Subject proportions of Biphentin[®] doses after one week of open-label treatment were: 20 mg (44%), 15 mg (25%), 50 mg (2%), and 60 mg (0%). The order changed after 11 weeks: 30 mg (28%), 40 mg (25%), 50 mg (18%), 20 mg (17%), and 60 mg (9%). No relationship was observed between final open-label dose and body weight (linear regression, $p = 0.1$).
- Biphentin[®] was well-tolerated. AEs were typical of those seen with other methylphenidate formulations commonly used for ADHD (no unexpected laboratory tests, vital signs, or ECG results).

II. INSPECTIONS

Four specific study-sites were audited at GCP inspection of three CI sites selected for large subject enrollment (one site with two studies). No concerns were identified at NDA review about study conduct, including CI conflict of interest. Study 001 was conducted entirely (only) at Site 01.

Clinical Investigator Site		Study, Site, Enrollment	Inspection Outcome
1	Sharon B. Wigal, Ph.D. University of California, Irvine 19722 MacArthur Boulevard Irvine, CA 92612	Study 001 (Site 01), 26 subjects 26 open-label, 22 blinded	December 8 – 16, 2014 Pending, preliminary NAI
2		Study 002, Site 01 29 subjects	
3	Ann C. Childress, M.D. 7351 Prairie Falcon Road, Suite 160 Las Vegas, NV 89128	Study 002, Site 03 39 subjects	November 18 – 24, 2014 Pending, preliminary NAI
4	Gregory G. Gunsten, M.D. Coastal Children's Clinic 703 Newman Road New Bern, NC 28562	Study 002, Site 16 40 subjects	October 27 – 30, 2014 Pending, preliminary NAI

NAI = no action indicated (no significant deficiencies); Pending = preliminary results based on communication with field investigator

1. Sharon B. Wigal, Ph.D. (Study 001)

a. What was inspected:

- Records review: local institutional review board (**IRB**) oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: subject randomization, major efficacy endpoints, AEs, protocol deviations, and subject discontinuations

b. General observations and comments:

Study 001, Site 01: 32 subjects were screened, 26 (open-label) and 22 (blinded) were enrolled, and 22 completed the study. Records were reviewed for all subjects (to include primary endpoint verification), including detailed review for 10 subjects completing the study.

No significant deficiencies were observed and a Form FDA 483 was not issued. Observed deficiencies were limited to two apparently minor and isolated SKAMP data entry errors for Subject 01, each discrepant by a score of 1 between the source record (correct) and the NDA data listing (incorrect). Site data were entered into the sponsor's database using web-based case report forms (**CRFs**).

All other audited data were verifiable between source records and NDA data listings. Study conduct appears adequate, including informed consent, AE reporting, and drug accountability. Study records were complete and well-organized. IRB oversight and sponsor monitoring appeared acceptable.

c. Assessment of data integrity: The data for this study from this CI site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

2. Sharon B. Wigal, Ph.D. (Study 002)

a. What was inspected: same as above for Study 001

b. General observations and comments:

Study 002, Site 01: 39 subjects were screened, 29 were enrolled, and 25 completed the study. Records were reviewed for all subjects (to include primary endpoint verification), including detailed review for 10 subjects completing the study.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following apparently minor and/or isolated deficiencies were verbally discussed: (1) one isolated unreported AE (headache), (2) one subject enrolled without urinalysis or urine drug testing, and (3) few subjects, unscheduled study visits, reasons not documented.

Reviewer Comments: These deficiencies appear to be minor isolated errors consistent with GCP: (1) the unreported headache was mild and resolved uneventfully; (2) negative urine test results were obtained three weeks later; and (3) the unscheduled study visits were to monitor AEs after an increase in the dose of the study medication for those subjects at increased risk for AEs (CI judgment).

Overall, the study conduct appears adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records appeared complete. All audited endpoint data were verifiable between source records and NDA data listings.

c. Assessment of data integrity: The data for this study from this CI site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

3. Ann C. Childress, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, and subject discontinuations

b. General observations and comments:

Study RP-BP-EF002, Site 03: 40 subjects were screened, 39 were enrolled, and 35 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 12 subjects.

No significant deficiencies were seen and a Form FDA 483 was not issued. Study conduct appears adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable between source records and NDA data listings.

c. Assessment of data integrity: The data from this CI site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

4. Gregory G. Gunsten, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records

- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 002, Site 16: 45 subjects were screened, 40 were enrolled, and 38 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 15 enrolled subjects.

No significant deficiencies were seen and a Form FDA 483 was not issued. The following observations were verbally discussed:

- Due to instability in electronic data capture (**EDC**) using web-based CRFs, the study data could not be reliably recorded electronically. At post-inspection correspondence with OSI, Rhodes claimed that all study sites in Study 002 had been instructed to use paper CRFs in lieu of EDC.

Reviewer Comments: The original data collection forms (DCFs) were used as CRFs, apparently with sponsor approval. Although DCFs are technically source documents, the DCFs for this study were useful also as efficient CRFs and obviated the need for manual data transfer (to new paper CRFs). This use of the DCFs as CRFs appears to be consistent with GCP in eliminating one major source of potential data transcription error without losing data recording accuracy or efficiency.

- Minor isolated data discrepancies between source documents and NDA data listings: (1) ADHD-RS-IV, Subject 39, Visit 3, one discrepancy (primary endpoint); (2) ADHD-RS-IV, Subject 07, Visit 4 and post-study follow up, six discrepancies; and (3) CGI-S, Subject 12, Visit 2, one discrepancy

Reviewer Comments: Since the sponsor performed data entry using DCFs used as paper CRFs, this deficiency observation is applicable to the sponsor and not to the CI site. For a major endpoint, discrepant data were limited to one isolated datum for Subject 39 (Visit 3 ADHD-RS-IV). The observed data discrepancies appear minor, isolated, or otherwise unlikely to be significant.

- CSHQ: Many possible data discrepancies between source documents and NDA data listings, including discrepancies for Subjects 26 and 37 at Visits 2 and 8

Reviewer Comments: This observation could not be verified at post-inspection correspondence with the sponsor. Per protocol, different numerical scales were (intended to be) used in coding CSHQ results: the word results “never,” “rarely,” “sometimes,” and “usually” were to be coded using the 0-3 or the 1-4 scale, and in the forward or the reverse direction for either scale. The CSHQ data about sleep quality were collected only as exploratory data without impact on the study outcome.

- Temperatures (as part of vital signs) and ECG results were not always documented in a way consistent with good recordkeeping practices: missing data or inadequate correction (white-out or write-over, no corrector initial or correction date).
- For Subject 05, an AE of “anger problems” noted at Visit 6 appears not to have been reported to the sponsor (not shown on the corresponding NDA listing).

All observed deficiencies appear minor, isolated, or otherwise unlikely to be significant. Study conduct appears adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appear acceptable. Source records appeared adequate. Other than as noted above, all audited endpoint data were verifiable between source records and NDA data listings.

c. Assessment of data integrity: The data from this CI site appear reliable.

Note: The observations noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Two pivotal studies support this NDA for Aptensio XR[®] (provisionally accepted trade name) for the treatment of ADHD. Study 001 was a randomized controlled cross-over study in 26 subjects at a single study site. Study 002 was a randomized controlled study in 230 subjects at 16 study sites. The two studies were audited at GCP inspections of three study sites selected for large subject enrollment. In total, four specific study-sites were audited (two studies at one of the three CI sites) to include a review of the case records for 134 subjects (52%), including complete review for 47 subjects (18%).

For all four study-sites, no significant deficiencies were observed and a Form FDA 483 was not issued. Minor deficiency observations were verbally discussed. The study conduct at all inspected study sites appeared adequate, including IRB oversight and sponsor monitoring of study conduct. Overall, the audited data were verifiable between source records and NDA data listings. The data from the inspected study sites appear reliable as reported in the NDA.

Note: For all CI sites, the final inspection outcome classification remains pending. The observations noted above are based on preliminary communication with the field investigator and/or preliminary review of the establishment inspection report (EIR). An addendum to this clinical inspection summary will be forwarded to the review division if the inspection outcome classification changes or if additional concerns of clinical or regulatory significance are identified upon receipt and/or completion of EIR review.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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/s/

JONG HOON LEE
03/03/2015

JANICE K POHLMAN
03/04/2015

KASSA AYALEW
03/04/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: January 27, 2015

Requesting Office or Division: Division of Psychiatry Products (DPP)

Application Type and Number: NDA 205831

Product Name and Strength: Aptensio XR (Methylphenidate Hydrochloride)
Extended-Release Capsules
10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, (b) (4)
(b) (4)

Product Type: Single Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Rhodes Pharmaceuticals L.P.

Submission Dates: June 18, 2014, September 5, 2014, and January 8, 2015

OSE RCM #: 2014-1707

DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Psychiatry Products asked the Division of Medication Error Prevention and Analysis (DMEPA) to review the proposed labels and labeling for Aptensio XR (Methylphenidate Hydrochloride) Extended-Release Capsules (NDA 205831) to determine if they are at risk for medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling noted the following areas of needed improvement:

1. In *Dosage and Administration*, Full Prescribing Information, there are references to pounds instead of kilograms.
2. The product administration instructions in *Dosage and Administration*, Full Prescribing Information lack prominence.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labeling where product information needs to be clarified or made more prominent in order to help ensure the safe use of the product. We provide

recommendations in Sections 4.1 and recommend they are implemented prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Dosage and Administration, Full Prescribing Information (SharePoint, January, 15, 2015)

1. We recommend removing all references to pounds and instead change to kilograms.
2. We recommend making the administration instructions, “Aptensio XR may be taken whole, or the capsule may be opened...” in *Dosage and Administration*, more prominent. Consider placing this information under a separate subheading.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Aptensio XR that Rhodes Pharmaceuticals submitted on September 5, 2014.

Table 2. Relevant Product Information for Aptensio XR	
Active Ingredient	Methylphenidate Hydrochloride
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.
Route of Administration	Oral
Dosage Form	Extended-Release Capsules
Strengths	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)
Dose and Frequency	(b) (4) Aptensio XR may be taken whole, or the capsule may be opened and the entire contents sprinkled onto (b) (4) applesauce. If the patient is using the sprinkled administration method, the sprinkled (b) (4) should be consumed immediately; it should not be stored. Patients should take the (b) (4) with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.
How Supplied	90-count bottles
Storage	20° to 25°C (68° to 77°F)
Container Closure	(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Aptensio XR labels submitted by Rhodes Pharmaceuticals on September 5, 2014 and January 8, 2015 and the working version of the Prescribing Information found in SharePoint on January 15, 2015.

- Container label
- Prescribing Information (no image)

G.2 Label Images (not to scale)

(b) (4)



1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/IS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
01/27/2015

IRENE Z CHAN
01/27/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205831 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Aptensio XR Established/Proper Name: methylphenidate hydrochloride Dosage Form: extended-release capsule Strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)		
Applicant: Rhodes Pharmaceuticals, L.P. Agent for Applicant (if applicable):		
Date of Application: June 18, 2014 Date of Receipt: June 18, 2014 Date clock started after UN:		
PDUFA Goal Date: April 18, 2015		Action Goal Date (if different): April 17, 2015
Filing Date: August 17, 2014		Date of Filing Meeting: August 11, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): ADHD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 104624				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
202100	Quillivant XR	NDF		9/27/2015	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

guidance? ¹ If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: N/A</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	already a CII
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Conditionally accepted 8/2/2013. Sponsor plans to submit TN separately, at a later time
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Yes, but not needed. DRISK comments conveyed in 74-day letter
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK (PLT)? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2/11/2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2014

BLA/NDA/Supp #: 205831

PROPRIETARY NAME: Aptensio XR

ESTABLISHED/PROPER NAME: methylphenidate HCl

DOSAGE FORM/STRENGTH: extended-release capsules

APPLICANT: Rhodes Pharmaceuticals, L.P.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): ADHD

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sandy Chang	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Cara Alfaro	Y
	TL:	Mark Ritter	Y
Clinical Pharmacology	Reviewer:	Andre Jackson	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	Jinglin Zhong	N
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ikram Elayan	Y
	TL:	Linda Fossom	Y
Statistics (carcinogenicity)	Reviewer:		

	TL:		
Product Quality (CMC)	Reviewer:	Rao Kambhampati	Y
	TL:	David Claffey	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Relative BA study of a single 80-mg dose of Biphentin® capsule, a single 80-mg dose of Biphentin capsule dosed as sprinkles versus reference 25</p>
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	mg Ritalin® IR administered 3 times daily. Comparative BA study of a steady-state of Biphentin 80 mg ER capsules versus Ritalin 25 mg IR.
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments List comments: 	<input type="checkbox"/> Not Applicable
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

permit review based on medical necessity or public health significance? Comments:	
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Mitchell Mathis, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): November 11, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p>

	<input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

SHIN-YE CHANG
08/26/2014