CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205831Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/18/2015
From	Lucas Kempf, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	205831
Applicant	Rhodes Pharmaceuticals L.P.
Date of Submission	06/18/2014
PDUFA Goal Date	04/18/2015
Proprietary Name / Established (USAN) names	Aptensio XR®
Dosage forms / Strength	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, (b) (4)
Proposed Indication(s)	1. ADHD
Recommended:	Approval

1. Introduction

The sponsor submitted a 505(b)(2) application for methylphenidate hydrochloride extended-release (ER) capsule formulation for the single daily dose treatment of Attention Deficit Hyperactivity Disorder (ADHD). The Reference Listed Drugs (RLD) is Ritalin® and Ritalin SR®. This formulation was approved by Health Canada in March, 2006 under the trade name of Biphentin®.

The ratio of immediate release methylphenidate to controlled release methylphenidate in the methylphenidate hydrochloride ER capsules is 40/60. Methylphenidate ER capsules contain single, multilayer controlled-release beads comprising approximately 40% immediate release and 60% controlled release layers of methylphenidate. The controlled-release layers are comprised of a (b) (4). This formulation provides the controlled release of the drug substance.

The Sponsor is seeking approval for (b) (4) capsules strengths: 10, 15, 20, 30, 50, 60, (b) (4). They only submitted clinical efficacy trial data to support for the 10, 15, 20, 30, 50, and 60mg doses.

There were two major areas of disagreement with the sponsor. (b) (4)
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These issues will be covered in more detail below.

2. Background

Methylphenidate is an approved drug for the treatment of ADHD since December 1955. Since that initial approval multiple formulations have been developed to attain differential exposure

profiles. The RLDs are labeled up to 60 mg. No other formulation contains higher amounts of methyphenidate except Concerta® which has a triphasic exposure peak as opposed to the biphasic peak of this product and other mixes immediate release and delayed release elements. The multiple available formulations are enumerated on page 8 of Dr. Alfaro's clinical review.

There was a PreNDA meeting scheduled in February, 2013. Preliminary comments were provided to the sponsor and the meeting was canceled. (b) (4) DPP stated that it was unlikely that the recommended daily dose could exceed 60 mg. The maximum daily dose for methylphenidate products in the US is 60 mg for children, adolescents, and adults (except for Concerta based on its unique exposure profile). In the Biphentin® Product Monograph, the maximum recommended daily dose for children and adolescents is 60 mg. In order to recommend in labeling (b) (4)

(b) (4) DPP stated that the time of onset is the first time point at which you have demonstrated efficacy (re: SKAMP total score) and the latest time point that you can refer to in labeling is the latest time point at which you have demonstrated efficacy.

(b) (4)

3. CMC/Device

The CMC review was conducted by R. Kambhampati. Facilities were inspected with no significant deficiencies noted. Refer to CMC review for a comprehensive analysis.

4. Nonclinical Pharmacology/Toxicology

Methylphenidate is a well characterized compound and no non-clinical studies were submitted. There are no outstanding issues. As stated in the non-clinical review submitted on March 18th, 2015 by Dr. Ikram Elayan;

The chemistry review team identified one degradation product (b) (4) that was specified at levels NMT (b) (4)%. However, the sponsor agreed to lower the specification levels of this enantiomer from NMT (b) (4)% to NMT (b) (4)%

(qualification threshold for degradation products in new drug products), as stated in their letter dated 9/18/2014. Consequently there are no non-clinical issues.

Review of the literature on non-clinical and clinical data by Maternal health reviewer Miriam Dinatale, D.O. finalized on March, 16th, 2015 concluded that Aptensio XR labeling is similar in content to Quillivant XR (methylphenidate hydrochloride) labeling, but has been updated to comply with the PLLR. This review of the literature for relevant data revealed no new data with methylphenidate use in pregnant or lactating women.

5. Clinical Pharmacology/Biopharmaceutics

Methylphenidate is a well characterized drug with several formulations. This review will be narrowly addressing the clinical pharmacology bridge studies reviewed by Andre Jackson, Ph.D. signed March 27th, 2015. (b) (4) I agree with OCP's major findings are excerpted and summarized below with minor additions for clarity:

1. An adequate link has been established between Aptensio ® capsule and Ritalin ® immediate release product, the reference list product, through a relative bioavailability study. This fact is clearly shown in Figure 1 of the Clinical pharmacology review on page 6.
2. At mean level, pharmacokinetic profiles in adults and in pediatric patients both show double peaks with similar shape; however, pediatric patients receiving different doses appear to show large variability in the shape of their respective mean pharmacokinetic profiles. The pharmacokinetic findings appear to support the extension of the indication from pediatric patients to adults. Since ADHD is first diagnosed as a child and continues for a small proportion of the patients into adulthood, initial registration is done in pediatrics. Dosing should be less variable in adults.
3. (b) (4)
4. The pharmacokinetic profile of Aptensio ® is consistent with the expectations for an extended-release formulation and is sufficient to support a once daily dosing.
5. Aptensio ® capsule can be administered as a whole capsule or sprinkled onto applesauce. The AUC, Tmax, and Cmax were overlapping in both conditions.
6. Aptensio ® may be given with or without food. It is advised that patients should establish a routine pattern with regard to meals. There is a smaller peak under the fed condition. So to insure consistence of dosing and therefor efficacy, it should be given consistently in one or the other conditions.
7. Patients should avoid alcohol while taking Aptensio ® due to dose dumping of 80% of the drugs within the first hour in 40% alcohol.

6. Clinical Microbiology

The product Quality Microbiology assessment for Microbial limits for methylphenidate hydrochloride extended release capsules was reviewed by John Metcalfe, Ph.D. and submitted on January 20th, 2015. He concluded that the microbiological quality of the drug product is controlled via a suitable testing protocol.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the statistical, clinical and clinical pharmacology reviews to support the efficacy. Registration was based on two trials, **RP-BP-EF001** and **RP-BP-EF002**. Short term duration of efficacy is established in ADHD by a simulated class room study with repeated testing over the day. The commonly used instrument is the SKAMP Total score at every time point. The long term efficacy is also necessary to establish in this class of medication and is typically established using the change from baseline of the ADHD-RS-IV total score.

Study **RP-BP-EF001** was a randomized, double-blind, cross-over study in 26 children (6 to 12 years) with ADHD. In this clinical trial, subjects received methylphenidate ER open-label for 2-4 weeks to determine the "optimal" dose. A two week double-blind phase followed in which subjects received one week of Aptensio XR® (the dose from the open-label phase) or placebo and then received the opposite treatment for another week. At the end of each week of treatment, the SKAMP rating scale was administered at multiple time points (up to 12 hours post dose) in an analog classroom setting. Statistically significant differences favoring Aptensio XR® were demonstrated for the primary efficacy endpoint, the SKAMP Total score averaged over all post dose time points (**p = 0.0001**). Statistically significant differences favoring Aptensio XR® were demonstrated for the key secondary endpoint, duration of efficacy as measured by the SKAMP Total scores at each time point. Detailed description of design and analysis can be found in the statistical and clinical reviews.

Study **RP-BP-EF002** was a randomized, double-blind, fixed-dose, parallel study in 230 children and adolescents (6 to 17 years) with ADHD. Subjects were randomized to one of 4 fixed doses of Aptensio XR® (10, 15, 20 or 40 mg/day) or placebo for one week. Statistically significant differences favoring Aptensio XR® were demonstrated on the primary efficacy endpoint, mean change from baseline on the ADHD-RS-IV Total score **(p = 0.0046**). Each Aptensio XR® dose was compared to placebo on the primary efficacy endpoint. Statistically significant differences favoring Aptensio XR® were demonstrated for the 20 mg dose (**p = 0.0145**) and 40 mg dose (**p = 0.0011**) only. This study also included an 11-week open-label phase in which subjects could receive Aptensio XR® up to 60 mg/day. Detailed description of design and analysis can be found in the statistical and clinical reviews

There was no evidence of subpopulation effects in either study.

[redacted] (b) (4)

(b) (4)

8. Safety

This a 505(b)(2) application with a well characterized drug. There is no new safety signal for this formulation. I believe that this formation is safe for use in children. The side effect profile in the submitted clinical trials for this formulation reflects the well-known side effect profile of this class. The submitted data base was adequate to reflect the side effect profile. From the pivotal ADHD efficacy trials, RP-BP-EF001 and RP-BP-EF002, a total of 256 unique subjects received at least one dose of Aptensio XR®. Doses ranged from 10 mg to 60 mg/day. By protocol design, no subjects weighing < 25 kg could receive > 40 mg/day during the dose optimization or double-blind phases of the pivotal trials, though they could receive a higher dose in the open-label extension phases. The extent of exposure across these two studies is 137.7 patient years. There were no deaths in the program. There were discontinuations for the typical reasons for this product; insomnia, nausea, decreased appetite, increased heart rate. In product labeling for the methylphenidate products, the following adverse events/clinical issues are listed in the Warnings and Precautions section: potential for abuse and dependence, serious cardiovascular reactions (e.g. sudden death, stroke, MI), blood pressure and heart rate increases, psychiatric adverse reactions (e.g. exacerbation of pre-existing psychosis, induction of a manic episode in patients with bipolar disorder, new psychotic or manic symptoms), suppression of growth, priapism and peripheral vasculopathy (including Raynaud's Phenomenon). The labeling of this product should reflect the known risks of the RLD and the class.

9. Advisory Committee Meeting

N/A

10. Pediatrics

ADHD is a diagnosis that is first made in childhood with a smaller proportion continuing into adulthood. Therefor it has been division policy to require registration trials to begin with trials of patients who ages are 6-18 years old since this is the primary intended population though the indication is for the illness. The registration trials are described above. This application triggered PREA as directed for a new dosage form. The sponsor submitted an iPSP for pediatric patients from the ages 4 to less than 6 years old.

A PERC meeting was held on March 11, 2015. PeRC agreed with a partial waiver of ages less than 4 years of age due to the impracticality of such trials. The PeRC agreed with a deferral for pediatric patients 4 to less than 6 years of age due to the expected difficulty in enrolling pediatric patients of this age, and the Division's limited experience with the study of ADHD in younger children (4 to less than 6 years old). The PeRC recommended that the Division add a long term safety study of these patients to the PREA requirement. The PeRC recommended that the PK study be modified by utilizing existing information obtained from older pediatric patients (6-9 year olds) in order to decrease the amount of PK sampling needed.

PeRC has the following proposed Pediatric Research Equity Act (PREA) Postmarketing Requirements.

A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A randomized, double-blind, placebo-controlled, flexible-dose titration study of methylphenidate hydrochloride extended-release capsules (Aptensio XR®) in children ages 4 to 5 years diagnosed with ADHD.
Final Protocol Submission Date: by December 31, 2015
Study/Trial Completion Date: by March 31, 2019
Final Report Submission: by December 31, 2019

A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A single-dose, open-label, randomized pharmacokinetic study of Aptensio XR® capsules in male or female children (4 to less than 6 years of age) with ADHD in fed condition
Final Protocol Submission Date: by March 31, 2015
Study/Trial Completion Date: by December 31, 2016
Final Report Submission: by June 30, 2017

A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A one year Pediatric Open-Label Safety Study for patients age 4 to 5 years (at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD.

11. Other Relevant Regulatory Issues

DSI inspections report was finalized on 3/19/2015 by Dr. Kassa Ayalew and no action was indicated.

12. Labeling

Labeling discussions are ongoing at this time but class labeling was applied (b) (4)

(b) (4) Indication in labeling will be for ADHD and the population studied will be described in the clinical trials area.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approve for the indication of ADHD

- Risk Benefit Assessment

The benefits outweigh the risks for all the proposed doses (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

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- Recommended Comments to Applicant

N/A

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/s/

LUCAS P KEMPF
04/15/2015

MITCHELL V Mathis
04/16/2015