# Joint Supervisory Memo

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| **Date** | *see electronic date* |
| **From** | Bernard Fischer, MD (Cross-Discipline Team Leader)<br>Tiffany R. Farchione, MD (Acting Division Director) |
| **Subject** | Joint Supervisory Memo |
| **NDA/BLA # and Supplement#** | NDA 205831, S-005 |
| **Applicant** | Rhodes Pharmaceuticals |
| **Date of Submission** | 03/30/2018 |
| **PDUFA Goal Date** | 06/14/2019 (3-month extension) |
| **Proprietary Name (code name)** | Aptensio XR (PRC-063) |
| **Established or Proper Name** | Methylphenidate HCL |
| **Dosage Form(s) and strengths** | Extended-release capsule: 10 mg |
| **Applicant Proposed Indication(s)/Population(s)** | (b) (4) |
| **Applicant Proposed Dosing Regimen(s)** | (b) (4) . |
| **Recommendation on Regulatory Action** | *Approve; limitation of use in patients younger than 6 years* |
| **Recommended Indication(s)/Population(s)** | *N/A* |
| **Recommended Dosing Regimen(s)** | *N/A* |

# 1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

| Benefit-Risk Integrated Assessment |
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| This supplement was to provide safety and effectiveness data on Aptensio XR for the treatment of ADHD in pediatric patients 4 to < 6 years old. Several design flaws made interpretation of the submitted efficacy data difficult. Other design flaws made it difficult to fully interpret the submitted safety data. However, the overwhelming blood pressure and weight loss safety signals led the Division to conclude that the risk did not justify the possible benefit in this patient population. Therefore, the Division is recommending a Limitation of Use statement be included in labeling. (Of note, this benefit-risk assessment is for this particular, long-acting product and does not include a benefit-risk assessment for stimulant treatment in 4- and 5-year-olds in general.) |

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%.<br>• It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior.<br>• These symptoms can cause significant impairment in academic and social functioning during critical years of development if left untreated. | ADHD is a prevalent condition in children and adolescents. In many cases, symptoms can continue into adulthood. ADHD symptoms can substantially compromise academic and work performance and can impair social development and relationships without treatment. |
| Current Treatment Options | • There are behavioral therapies available as first-line treatments for patients ages 4 to < 6 years with ADHD.<br>• There are several products that have demonstrated safety and effectiveness in the treatment of ADHD, but there is little controlled data on stimulant treatment in patients 4 to < 6 years old.<br>• Most of these products contain amphetamine salts or methylphenidate. | There are several approved products for the treatment of ADHD. These are available as solid or liquid formulations, have different dosing regimens, and allow for different methods of oral administration to accommodate the needs of the individual patient. However, there is little data on the use of stimulants in patients ages 4 to < 6 years old. Despite this lack of data, stimulants are commonly prescribed to patients in this age range. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • More recently approved products contain atomoxetine or guanfacine.<br>• These products display differences in time to therapeutic onset, duration of action, or both; these differences are tightly linked differences in their pharmacokinetic profiles. Some products require more than one dose per day because of a short duration of action.<br>• Products have been developed as different formulations (tablets, capsules, or oral suspensions), which allow for different modes of oral administration (sprinkling on food, chewing, swallowing intact pills or capsules). | |
| Benefit | •Based on the Applicant's pre-specified analysis, Aptensio XR demonstrated statistically significant and clinically meaningful improvement over placebo in ADHD symptoms from baseline to 2 weeks at a mean dose of 26 mg (range 10 to 40 mg).<br>•The Agency's analysis supported the conclusion of efficacy. | The Applicant did not submit the statistical analysis plan to the Agency for final agreement. The protocol specified that after 1 week of the 2-week-long double-blind treatment, patients not meeting a certain threshold of symptom reduction could be transferred to the open-label protocol. These "transfers" were not considered early terminations. Data from these patients, collected during Visit 14, was intentionally miscoded as having been collected at Visit 15. In addition to treating the data from these patients as "last observation carried forward" (a statistical technique not acceptable to the Agency), this conduct violated the principle of randomization and the premise of "missing at random" in the subsequent analyses. The Agency's re-analysis (coding values for the visit when they occurred) supported Aptensio XR's efficacy but, due to the violations to underlying statistical principles, the Biometrics reviewer was unwilling to definitively conclude that Aptensio XR was effective. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk and Risk Management | • The nature of the observed adverse reactions with Aptensio XR was consistent with the simulant drug class.<br>• There were high rates of psychiatric adverse events, instances of elevated blood pressure, and weight loss in this patient population. | The interpretation of adverse events is complicated by the study design: Patients completed a 6-week, open-label "dose optimization" phase before being randomized to Aptensio XR or placebo. Patients with tolerability issues could therefore exit the study prior to reaching the double-blind phase. The rate of psychiatric adverse events during the open-label phase was high, but not inconsistent with the rates seen in pediatric patients ages 6 to 12 years treated with stimulants. The psychiatric adverse events had resolved at the time of the double-blind phase. The rates of elevated blood pressure (≥95$^{th}$ percentile by age, sex, and height) and weight loss, however, were inconsistent with rates observed in 6- to 12-year-olds on stimulants. Because of the disproportionate rates of these concerning adverse events, the Division will place a limitation of use for this age group in section 1 of labeling and describe the safety findings in section 8.4. |

# 2. Background

FDA approved Aptensio XR for the treatment of ADHD in patients 6 years and older on April 17, 2015. Pediatric Research Equity Act postmarketing requirements (PMRs) included studies for patients with ADHD ages 4 to < 6 years:

- A pharmacokinetic (PK) study (RP-BP-PK003)
- An efficacy and safety study (RP-BP-EF003)
- An open-label safety study (RP-BP-EF004)

This supplement was submitted in response to those PMRs.

The Applicant submitted the protocol for RP-BP-EF003 under IND 104624 on August 10, 2015. It was amended in August 2015 and December and February 2016.

Written Request

In January 2016, the Applicant submitted a Proposed Pediatric Studies Request. In response, the Agency issued a pediatric Written Request (WR) on May 11, 2016. It specified that a randomized, double-blind, placebo-controlled trial with a duration of at least 6 weeks in preschool-aged children (ages 4 and 5 years) and a flexible dose titration dosing scheme could acceptably demonstrate efficacy and safety. On June 9, 2016, the FDA requested a detailed statistical plan for review, and that this should include an interim analysis to be agreed upon prior to initiation of the study.

On October 18, 2016, the Applicant submitted a draft SAP and requested that the Agency amend the WR (b) (4) to allow a 6-week, open-label, dose-optimization phase followed by a 2-week, double-blind treatment phase in the acute efficacy and safety study. The Agency responded on February 2, 2017, indicating disagreement with this strategy (such a study design would enrich the double-blind phase with patients who tolerated and responded to the drug). The Agency countered that a flexible dose design would be acceptable, but that the treatment should be double-blind and placebo-controlled to ensure that safety data is collected from a non-enriched population.

At a guidance meeting held on November 29, 2017, this disagreement was re-iterated.
In the meeting minutes, FDA stated that:

- "We do not agree with a study design that would involve a very short period of double-blind, placebo-controlled treatment."

- "…we do not agree with the strategy of an open-label, dose-optimization phase followed by a double-blind treatment phase. We remain concerned that this strategy would result in a double-blind phase enriched for patients who tolerated and responded to the drug…, we want to ensure that you collect sufficient data to make meaningful safety comparisons between a drug-treated group and a placebo group".

- "We recommend a study design that is double-blind and placebo-controlled from the beginning of the study."

- "We believe that a trial duration of 6 weeks for Study RP-BP-EF003 would provide sufficient safety and efficacy data…"

At this meeting, the Applicant reported that they had already initiated Study RP-BP-EF003 in response to PREA requirements. FDA expressed uncertainty as to whether the completed study would be sufficient to fulfill the Written Request; stating, "Our primary concern is whether the completed study provides sufficient safety data." The FDA advised the Applicant to submit a new request to amend the WR and the Agency revised the WR (issued June 18, 2018).

When the Pediatric Exclusivity Board examined the results of the studies, they and the Division found several deviations from the requirements of the WR (e.g., number of patients completing Study RP-BP-EF004 at the time of the supplement's submission was 31 versus the 50 required by the WR). However, because of the magnitude of the safety signal from the use of Aptensio XR in this patient population, the Division felt the studies could provide information for labeling. Therefore, the Committee granted exclusivity.

Inspections

The Office of Scientific Investigation inspected Sites 07, 09, and 12 (all three sites provided enrollment for RP-BP-EF003 and -004). In the course of these inspections, the Agency discovered that the Applicant had changed the criteria for reporting hypertension (HTN) as an adverse event (AE) several times during the study by way of letters to the investigators:

- Initial Protocol: blood pressure ≥ 95th percentile for age, gender and height (no mention of how many occurrences constituted a HTN AE)
- July 12, 2017 Letter: Each occurrence of blood pressure ≥ 95th percentile was a HTN AE
- July 31, 2017 Letter: Three separate occurrences of blood pressure ≥ 95th percentile defined a HTN AE

Investigators who had determined that a HTN AE had occurred were later instructed to remove the AE if it did not fit the definition from the July 31 Letter. This potentially introduced bias in the evaluation and reporting of elevated blood pressure readings as HTN AEs. The AE of weight loss was similarly revised to become three separate occurrences of weight loss. An information request was sent to the Applicant to justify the changes to the HTN and weight loss definitions and to evaluate how these changes might have affected AE reporting. The Applicant's response was received on the Supplement's initial goal date. To give the review team time to evaluate the Applicant's response, the response was coded as a major amendment and the goal date extended by the standard 3 months. Ultimately, the review team decided that, although the Applicant's AE numbers for HTN and weight loss might be inaccurate, the record

of all blood pressure measurements and weights from the study visits in the VS Database was sufficient for a safety analysis.

Of note, the change communicated to the investigators in the July 31 Letter was approved by the Studies' Institutional Review Board on October 31, 2017. Study RP-BP-EF003 was completed November 2, 2017. Therefore, the Applicant's changes (as communicated to investigators via the letters) were not IRB-approved at the time they were implemented. However, this violation of Good Clinical Practice did not appear to alter the studies' integrity.

# 3. Product Quality

The product quality review was performed by primary reviewer Lin Qi and secondary reviewer Branch Chief David Lewis. They conclude that the supplement did not provide for any changes to the chemistry, manufacturing, or controls of the drug product and there were no changes proposed to CMC labeling information. They recommend approval.

# 4. Nonclinical; Pharmacology/Toxicology

The primary pharmacology/toxicology reviewer was Deepa Rao; the secondary reviewer was Pharmacology Supervisor Ikram Elayan.

The Applicant did not submit any nonclinical studies. The nonclinical team revised the relevant sections of labeling for consistency with other, recently approved stimulant products.

# 5. Clinical Pharmacology

The primary Clinical Pharmacology reviewer was Di Zhou; the secondary reviewer was Team Leader Luning (Ada) Zhuang. Their findings are as follows:

- The overall exposures (AUC0-inf and AUC0-t) increased by 2 to 3 fold in pediatric patients 4 to under 6 years compared with adults and pediatric patients 6 to12 years.
- An approximately 2-fold increase in Cmax was also observed in pediatric patients 4 to under 6 years as compared to adults and pediatric patients 6 to 12 years.
- Tmax to reach the first peak across different populations are similar (2 to 3 hrs). Longer half-life was observed in pediatric patients 4 to under 6 years compared with adults and pediatric patients 6 to 12 years.
- Time to reach the second peak was observed at approximately 10 to 12 hours, which was delayed compared with adults and pediatric patients 6 to 12 years of age (~ 8 hours).

The Clinical Pharmacology Team recommends approval with the addition of age-related pharmacokinetic data in labeling. However, because of the limitation of use, the pharmacokinetic data will not appear in labeling.

# 6. Clinical Microbiology

There were no clinical microbiology concerns with this supplement.

# 7. Clinical/Statistical Efficacy

The primary clinical reviewer was John Umhau; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Eiji Ishida; the secondary reviewer was Team Leader Peiling Yang.

In Dr. Umhau's review, he documents his belief that there is no clinical benefit from treating patients in this age group because they are not yet in a school setting. He believes any benefit from treatment would be solely for the parents of a child with ADHD (e.g., a child would not be expelled from daycare). We do not agree. Children (including preschool-aged children) with ADHD often have impulse-control problems. Coupled with hyperactivity, these children are at risk for accidents (e.g., falls from inappropriate climbing, darting into traffic). Children with untreated ADHD are also at risk for impaired social development (e.g., alienating peers during a critical period of relationship development). Therefore, we believe that effective ADHD treatment for this age group does have a public health benefit.

The Applicant conducted an acute efficacy study (RP-BP-EF003) with three phases:

1. A 6-week, Parent Training Phase with no medication intervention
2. A 6-week, open-label, "Dose-optimization" Phase
3. A 2-week, randomized, placebo-controlled, Double-blind Phase

The primary endpoint was the difference in the ADHD Rating Scale-IV (ADHD-RS-IV) from the baseline of the Double-blind Phase to 2 weeks (the end of the Double-blind Phase).
See Table 1 for the disposition of patients during the Study.

**Table 1. Disposition of Patients during RP-BP-EF-003; n.**

| | Aptensio XR | Placebo | Total |
|---|---|---|---|
| Screened | - | - | 194 |
| Enrolled | - | - | 158 |
| *Entered Parent Training Phase* | - | - | *132* |
| *Bypassed Parent Training Phase* | - | - | *20* |
| Eligible for Open-label Phase | - | - | 128 |
| Entered Open-label Phase | - | - | 119 |
| Randomized in Double-blind Phase | 40 | 50 | 90 |
| Study Completers | 38 | 48 | 86 |

Dr. Umhau mentions the lack of a washout period between the Dose-optimization Phase and the Double-blind Phase as a major design flaw. He contends that stimulant withdrawal might be confused with symptom return in the placebo group. We do not feel that the symptoms of stimulant withdrawal would mirror ADHD symptoms enough and extend long enough to be a significant source of confounding at the Double-blind Phase Week 2 assessment.

On November 2, 2018, the Applicant noted that 14 of the 90 subjects randomized to the Double-blind Phase of Study RP-BP-EF003 did not meet eligibility criteria (intended to remove open-label non-responders from the double-blind phase of the study). The Agency determined that this protocol violation had little impact on the Applicant's results (as with the lack of a washout period, if it were to affect the efficacy determination, it would make it more difficult to separate from placebo).

The Applicant did not submit the statistical analysis plan to the Agency for final agreement. The protocol specified that after 1 week of the 2-week-long double-blind treatment period, patients not meeting a certain threshold of symptom improvement could be transferred to the open-label protocol at investigator discretion. These "transfers" were not considered early terminations. Data from these patients, collected during Visit 14, was intentionally miscoded as having been collected at Visit 15. The data at Visit 15 from these patients were imputed using a "last observation carried forward" approach, which would require a very strong assumption (*missing completely at random*) about missing data. This assumption was violated because these patients were discontinuation for a particular reason (lack of efficacy). Twenty-nine patients (10 Aptensio XR and 19 placebo) were transferred to the long-term extension study in this way. Of note, biometrics reviewer Mr. Ishida also determined that, of the 29 patients transferred to the open-label protocol, only 23 should have been transferred based on the Applicant's protocol. Additionally, four patients who met the criteria for transfer to the open-label protocol were not transferred and remained in the Double-blind Phase.

The Applicant's initial analysis (equivalent to using a last observation carried forward approach to impute the Visit 15 data for the 29 patients progressed to the open-label study early) and a post-hoc analysis (only patients with data from both Visits 14 and 15) are presented in Table 2.

**Table 2. Applicant's Efficacy Analysis; Study RP-BP-EF003.**

| **ADHD-RS-IV Total Score** | **Aptensio XR** (n=39) | **Placebo** (n=50) |
|---|---|---|
| **Initial Analysis** | | |
| Mean change from baseline (SD) | 6.3 (12.3) | 17.3 (16.8) |
| LS Mean (SE) | 5.7 (2.5) | 16.9 (2.3) |
| 95% CI (placebo-Aptensio XR) | -18.0, -4.4 | - |
| p-value | 0.002 | - |
| **Post-hoc, Visit 15 Patients[a]** | | |
| Mean change from baseline (SD) | 2.1 (9.2) | 10.5 (15.2) |
| LS Mean (SE) | 2.1 (2.4) | 10.5 (2.4) |
| 95% CI (placebo-Aptensio XR) | -15.2, -1.6 | - |
| p-value | 0.016 | - |

[a]Including only those patients with data from Visits 14 and 15.

Because the implicit assumption about missing data in the Applicant's primary analysis appears to be violated, the FDA biometrics reviewer Mr. Ishida performed post-hoc analyses,

including a commonly adopted analysis based on Mixed Model Repeated Measures (MMRM) to assess the impact of the missing data (discontinuation) on the efficacy outcome. Table 3 summarizes the results from the MMRM analysis, which requires less rigorous assumption about missing data. The results support the finding from the Applicant's primary analysis in that efficacy was demonstrated given the pre-specified randomized withdrawal-type design.

**Table 3. FDA re-analysis of Efficacy Data, Study RP-BP-EF003.**

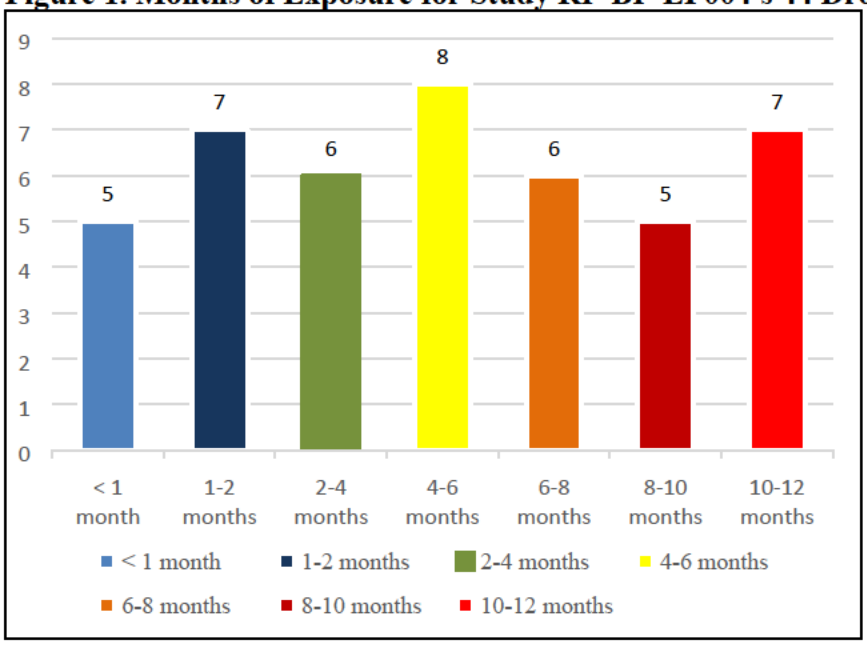
| ADHD-RS-IV Total Score | Aptensio XR (n=39) | Placebo (n=50) |
|---|---|---|
| LS Mean (SE) | 5.3 (2.4) | 16.2 (2.2) |
| 95% CI (placebo-Aptensio XR) | -17.4, -4.4 | - |
| p-value | 0.001 | - |

# 4. Safety

The primary clinical reviewer was John Umhau; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer. Biometrics reviewer, Eiji Ishida, also completed safety analyses in the primary clinical review.

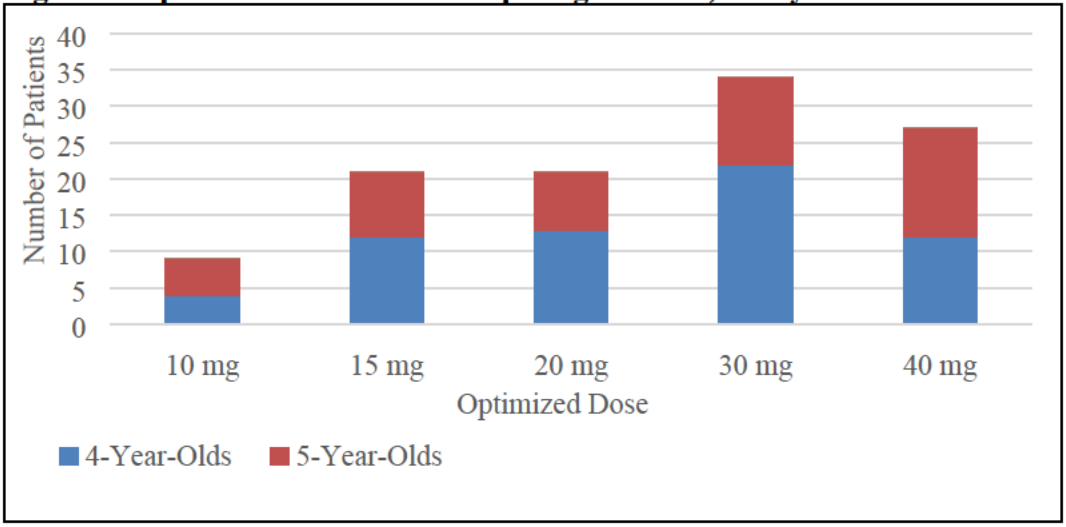
The safety analysis is based on Studies RP-BP-EF003 and RP-BP-EF004. Study RP-BP-EF004, the 12-month open-label extension study, enrolled 89 patients. Of those, 31 patients had completed the study at the time of the Supplement's submission (see Figure 1 for months of exposures from patients terminating the study early). After the Supplement was submitted, an additional 13 patients completed Study RP-BP-EF004 with 12-month data. Data from these 13 additional completers was submitted to the Agency on March 19, 2019.

**Figure 1. Months of Exposure for Study RP-BP-EF004's 44 Drop-outs; n.**



The mean dosage of the 112 patients completing Study RP-BP-EF003's Dose-optimization Phase was 26 ± 10 mg daily. See Figure 2 for the range of optimized doses for patients by age. These optimized doses were continued during Study RP-BP-EF003's Double-blind Phase and during Study RP-BP-EF004.

**Figure 2. Optimized Dose for Participating Patients; Study RP-BP-EF003.**




A dose-optimization period prior to randomization makes it difficult to evaluate safety. Patients with intolerable adverse events may drop out of the study prior to randomization but, because there is no comparison group, it is not easy to establish causality. Without fixed doses, it is impossible to determine a dose-response for observed adverse events. During the open-label, Dose-optimization Phase, adverse events reported in > 5% of patients included: insomnia (23%), infection (22%), decreased appetite (20%), decreased weight (18%), irritability (including aggression, anger, and negativism) 18%, hypertension (13%), affect lability (10%), abdominal pain (9%), emotional disorder (8%), headache (8%), pyrexia (5%), and vomiting (5%). Twelve patients discontinued treatment during the open-label phase because of adverse events: irritability/aggression (4), affect lability (3), emotional disorder (2), hypertension (1), insomnia (1), and nausea (1).

The Applicant changed the definition of hypertension and weight loss AEs during the studies and removed some reports of these AEs from the AE database (as detailed in Section 2. *Background*). Because the raw blood pressures and weights were reported in the vital signs database, whether the values were labeled as AEs is not vital to interpreting the safety data.

Table 4 shows the AEs reported in ≥ 2% of patients in the 6-week, Dose-optimization Phase compared to the 6-week Parent Training Phase (without medication). Of note, the Parent Training Phase included four visits while the Dose-optimization Phase had six visits; therefore, there were additional opportunities to identify AEs during the Dose-optimization Phase.

**Table 4. Adverse Events Occurring in ≥2% Patients on Open-Label Aptensio XR versus No Medications, Study RP-BP-EF003.**

| Adverse Reaction | Aptensio XR Open-Label Dose-Optimization Phase: 6 weeks (n=119[a]) | Parent Training Phase (No Medication): 6 weeks (n=119[a]) |
|---|---|---|
| **Cardiac Disorders/Vascular Disorders** | | |
| Hypertension; systolic hypertension[b] | 15 (13%) | 6 (5%) |
| Tachycardia | 2 (2%) | 0 |
| **Gastrointestinal Disorders** | | |
| Abdominal pain; abdominal pain, upper | 11 (9%) | 0 |
| Vomiting | 6 (5%) | 1 (1%) |
| Diarrhea | 5 (4%) | 1 (1%) |
| Flatulence | 2 (2%) | 0 |
| Nausea | 3 (3%) | 0 |
| **General Disorders** | | |
| Fever (pyrexia) | 6 (5%) | 3 (3%) |
| Crying | 3 (3%) | 0 |
| **Investigations** | | |
| Weight decreased[b] | 20 (17%) | 0 |
| **Metabolism and Nutrition Disorders** | | |
| Decreased appetite | 24 (20%) | 0 |
| **Musculoskeletal Disorders** | | |
| Pain in extremity | 2 (2%) | 0 |
| **Nervous System Disorders** | | |
| Headache | 9 (8%) | 0 |

**Table 4. continued.**

| Adverse Reaction | Aptensio XR (n=119[a]) | No Medication (n=119[a]) |
|---|---|---|
| **Psychiatric Disorders** | | |
| Insomnia; initial insomnia; middle insomnia | 27 (23%) | 2 (2%) |
| Irritability; aggression; anger, negativism | 21 (18%) | 0 |
| Affect lability; mood swings | 14 (10%) | 0 |
| Emotional disorder | 13 (10%) | 0 |
| Somnolence | 2 (2%) | 0 |
| Dermatillomania | 2 (2%) | 0 |
| Dysphemia | 2 (2%) | 0 |
| Social avoidant behavior | 2 (2%) | 0 |
| **Renal and Urinary Disorders** | | |
| Enuresis | 2 (2%) | 1 (1%) |
| **Respiratory, Thoracic, and Mediastinal Disorders** | | |
| Epistaxis | 3 (3%) | 0 |
| Rhinorrhea | 2 (2%) | 1 (1%) |

[a]The same patients are in both phases.
[b]The actual numbers of blood pressure and weight loss AEs are likely higher than reported because of the Applicant's reclassification of how these AEs were counted during the study. See discussion below for more details.

Table 5 shows the AEs occurring in ≥2% patients on Aptensio XR versus placebo during the Double-blind Phase of Study RP-BP-EF003.

**Table 5. Adverse Events Occurring in ≥2% Patients on Aptensio XR versus Placebo during the 2-week Double-blind Phase of Study RP-BP-EF003.**

| Adverse Reaction | Aptensio XR (n=40) | Placebo (n=50) |
|---|---|---|
| Hypertension[a] | 3 (8%) | 0 |
| Pollakiuria; urinary incontinence | 2 (5%) | 0 |
| Formication | 1 (3%) | 0 |
| Decreased Appetite | 1 (3%) | 0 |
| Emotional poverty | 1 (3%) | 0 |
| Negativism | 1 (3%) | 0 |
| Onychophagia | 1 (3%) | 0 |
| Tachycardia | 1 (3%) | 0 |

[a]The actual numbers of blood pressure AEs are likely higher than reported because of the Applicant's reclassification of how this AEs were counted during the study. See discussion below for more details.

Psychiatric AEs

In Dr. Umhau's review, he spends considerable time discussing psychiatric AEs in this patient population. He contends that there are significantly more psychiatric AEs in preschool children than in school-aged children when taking methylphenidate. He supports this by referencing the

incidence of psychiatric AEs during Study RP-BP-EF003's open-label, Dose-optimization Phase compared to the Parent Training (no medication) Phase, and by references to published academic studies. He cites a rat study showing exposure to methylphenidate can alter the blood-brain barrier and that adult rats exposed to methylphenidate as pups can have learning problems. His ultimate concern is that preschool children exposed to methylphenidate will develop alterations in the blood-brain barrier leading to neuroinflammation and subsequent irreversible neuropsychiatric sequelae.

There have been no head-to-head comparisons of AE rates in preschoolers compared to school-aged children (including the published academic literature). In the open-label phase of RP-BP-EF003, 40% of the patients had a psychiatric AE. In the 2- to 4-week open-label phase of RP-BP-EF001 (Aptensio XR in ages 6 to <13 years), 50% of the patients had a psychiatric AE. In the 11-week open-label phase of Study RP-BP-EF002 (Aptensio XR in ages 6 to <18 years), 21% of patients had a psychiatric AE. Comparisons of psychiatric AEs during open-label, dose-optimization phases for several stimulant trials are shown in Table 6. As illustrated, the picture is not as simple as more psychiatric AEs in preschoolers. Some psychiatric AEs are more common in preschoolers, some are less common, depending on the studies that are compared, their enrollment, their length, et cetera. However, the type of observed psychiatric AEs are the same across ages (i.e., there are no unique psychiatric AEs in the preschool age group).

**Table 6. Incidence of Psychiatric AEs During Dose-optimization for Several Stimulant Trials Submitted to FDA.**

| AE Term | 4 to >6 years | 6 to >13 years | | | | |
|---|---|---|---|---|---|---|
| | Methylphenidate | | | | | Amphetamine |
| | Aptensio XR Study -003 | Aptensio XR Study -001 | Quillichew | Jornay PM Study 1 | Jornay PM Study 2 | Evekeo |
| Insomnia[a] | 23% | - | 11% | 33% | 34% | 10% |
| Irritability[b] | 18% | 19% | - | - | 5% | 14% |
| Affect Lability | 10% | 12% | 12% | 26% | 17% | 9% |
| Emotional Disorder | 8% | 8% | - | - | - | - |

[a]Includes initial insomnia, middle insomnia, and terminal insomnia.
[b]Includes aggression, anger, and negativism.

Regarding Dr. Umhau's concern that the psychiatric AEs are the result of irreversible neuroinflammation, the relevance of his referenced rat study to humans with ADHD is unknown. The observation that psychiatric AEs in Study RP-BP-EF003 had largely resolved by the time of the double-blind phase (see Table 5) is inconsistent with a lifelong deficit. Admittedly, preclinical studies supporting the long-term psychiatric safety of CNS-active drugs is lacking—but this is the case with all age groups and medications and is not unique to

this application. As with every medical decision, whether to prescribe CNS-active medications to children is a consideration of risks and benefits weighing both the known and the unknown.

In summary, we do not feel the psychiatric AEs in this population represent a unique or excessive risk compared to the psychiatric AEs in school-aged children.

Diversion and Addiction

In Dr. Umhau's review, he reports "it is likely from the case report descriptions that several subjects left the study because of 'compliance' with medication that was related [to] the diversion of Aptensio XR for illicit use (Clinical Review, p. 57)." He believes that some parents likely manufactured or exaggerated their children's symptoms in order to have access to stimulant medications. His belief is based on the fact that ten patients were withdrawn from the study early for "compliance" issues.

This is a serious assumption and not supported by the data. In our previous experience, early patient withdrawals for compliance issues are almost universally related either to the patient not taking their study drug or not coming to required appointments. There is no indication that the compliance cases Dr. Umhau references were anything other than patients not taking study drug. It is worth noting that parents wishing to divert their child's medications for illicit use would face less scrutiny (and no chance of receiving a placebo) in clinical care rather than a drug trial.

Dr. Umhau recommends implementing a Risk Evaluation and Mitigation Strategy (REMS) to prevent parents' abuse of their children's stimulant medication. The problems with this proposal are:

1. Diversion of prescription medications is a public health problem beyond stimulants and beyond a parent-child relationship. A solution to diversion must, by regulation, involve the Drug Enforcement Agency and likely the entire healthcare industry; it is beyond the scope of this one application.
2. A REMS is put into place to ensure patient safety. Preventing a parent's diversion of their child's stimulant prescription does not fall into the authority or purpose of a REMS.
3. We have no evidence that parental diversion of a child's stimulant prescription is a widespread phenomenon (or that it occurred in these studies).

Dr. Umhau opines that "there is also the potential that administering MPH [methylphenidate] to this vulnerable population will promote their future addiction to stimulants (Clinical Review, p. 90)." In fact, there is strong evidence that patients' risk of developing substance use disorders is decreased with effective ADHD treatment—and that earlier treatment is more protective (McCabe SE, Dickinson K, and Wilens TE. Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: A multi-cohort national study. J Am Acad Child Adolesc Psychiatry 2016; 55:479-86.).

Hypertension

As discussed in the *Background* section, the Applicant changed how hypertension AEs were defined during the Studies. However, given the Agency had the raw blood pressure data, we were able to draw our own conclusions regarding blood pressure AEs for preschool-aged patients.

Comparing the no-medication Parent-training Phase to the open-label Dose-optimization Phase in Study RP-BP-EF-003, there were more males with blood pressures at or above the 95$^{th}$ percentile (for age, sex, and height) on Aptensio XR then when on no medication (Table 7). In females, the opposite pattern emerged for diastolic blood pressures.

**Table 7. Elevated Blood Pressures During Study RP-BP-EF-003.**

| Population and Measure | Aptensio XR Open-Label Dose-Optimization Phase: 6 weeks | Parent Training Phase (No Medication): 6 weeks |
|---|---|---|
| **Males** (n=90) | | |
| Elevated Systolic Blood Pressure; n (%) | 37 (41%) | 24 (27%) |
| Elevated Diastolic Blood Pressure; n (%) | 50 (56%) | 41 (46%) |
| Elevated Systolic or Diastolic; n (%) | 58 (64%) | 48 (53%) |
| **Females** (n=27) | | |
| Elevated Systolic Blood Pressure; n (%) | 6 (22%) | 3 (11%) |
| Elevated Diastolic Blood Pressure; n (%) | 7 (26%) | 11 (41%) |
| Elevated Systolic or Diastolic; n (%) | 8 (30%) | 12 (44%) |

During Study RP-BP-EF-003's Double-blind Phase, more children had blood pressures at or above the 95$^{th}$ percentile (for age, sex, and height) on Aptensio XR than placebo (Table 8). Instances of elevated blood pressures continued in a large percentage of consented patients during the open-label extension study (RP-BP-EF-004).

**Table 8. Elevated Blood Pressures During Double-blind Phase of Study RP-BP-EF-003 and Study RP-BP-EF-004.**

| Measure | RP-BP-EF-003 | | RP-BP-EF-004 |
|---|---|---|---|
| | Aptensio XR n=39 | Placebo n=50 | Aptensio XR n=90 |
| Elevated Systolic Blood Pressure; n (%) | 12 (30%) | 4 (8%) | 42 (47%) |
| Elevated Diastolic Blood Pressure; n (%) | 19 (49%) | 18 (36%) | 65 (72%) |
| Elevated Systolic or Diastolic; n (%) | 21 (54%) | 19 (38%) | 72 (80%) |

These rates of elevated blood pressures are higher than those typically seen in school-aged children in stimulant studies.

Weight loss

During Study RP-BP-EF-003's 6-week, open-label Dose-optimization Phase, 35% of the patients experienced weight loss (N=119). The average weight loss in those patients was 0.68 kg, but eleven patients lost more than 1 kg.

In order to examine long-term weight loss in 4- to < 6-year old patients, we compared the weights of patients at Visit 6 in Study RP-BP-EF-003 (after at least 6 weeks of no medication during the Parent Training Phase) to Visit 24 in Study RP-BP-EF-004 (after 12 months of Aptensio XR). Patients' age and weight (in kilograms) was entered into an online calculator (medcalc.com/growth), which produced a U.S. Centers for Disease Control growth chart for weight. Given the inherent imprecision in determining the value for points that are not on the prespecified curves (i.e., the 5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 90$^{th}$, and 95$^{th}$ percentiles), the following approximations were made:

| For points between: | Approximated value: |
|---|---|
| *5$^{th}$ and 10$^{th}$ percentile curves* | *7$^{th}$ percentile* |
| *10$^{th}$ and 25$^{th}$ percentile curves* | *15$^{th}$ percentile* |
| *25$^{th}$ and 50$^{th}$ percentile curves* | *40$^{th}$ percentile* |
| *50$^{th}$ and 75$^{th}$ percentile curves* | *60$^{th}$ percentile* |
| *75$^{th}$ and 90$^{th}$ percentile* | *80$^{th}$ percentile* |
| *90$^{th}$ and 95$^{th}$ percentile* | *92$^{nd}$ percentile* |

Five patients who completed RP-BP-EF-004 were enrolled from the pharmacokinetic study (RP-BP-PK003). Of the 39 patients who completed both RP-BP-EF-003 and -004, there were 20 whose weight percentile decreased by at least 10 percentiles over the course of 12 months on Aptensio XR (i.e., patients who "fell off their growth curve"). These patients are presented in Table 9.

**Table 9. Patients with Weight Decrease by 10 Percentiles over 1 Year on Aptensio XR.**

| Subject ID | Sex | RP-BP-EF-003 Visit 6 Weight Percentile | RP-BP-EF-004 Visit 24 Weight Percentile | Percentile Change |
|---|---|---|---|---|
| (b) (6) | F | 60 | 25 | -35 |
| | M | 90 | 75 | -15 |
| | M | 75 | 50 | -25 |
| | M | 50 | 25 | -25 |
| | F | 92 | 80 | -12 |
| | M | 75 | 60 | -15 |
| | M | 40 | 25 | -15 |
| | M | 90 | 50 | -40 |
| | M | 80 | 60 | -20 |
| | F | 90 | 75 | -15 |
| | M | 75 | 60 | -15 |
| | M | 15 | 5 | -10 |
| | F | 80 | 40 | -40 |
| | M | 90 | 75 | -15 |
| | F | 95+ | 80 | -15+ |
| | M | 90 | 60 | -30 |
| | M | 50 | 40 | -10 |
| | M | 95 | 80 | -15 |
| | F | 92 | 50 | -42 |
| | M | 90 | 60 | -30 |

Patients losing weight on Aptensio XR were not restricted to those at the higher end of the weight growth curve; patients below the 50$^{th}$ percentile also lost weight.

## 5. Advisory Committee Meeting

This section is not applicable to this application.

## 6. Pediatrics

See Sections 7 and 4 for a review of the effectiveness and safety in pediatric patients.

## 7. Other Relevant Regulatory Issues

None.

# 8. Labeling

The Division has decided that the possible benefits do not outweigh the risks for Aptensio XR treatment of ADHD in ages 4 to < 6. Therefore, a brief summary of weight data was added to section 8.4 along with a limitation of use.

# 9. Postmarketing Recommendations

Dr. Umhau suggests several postmarketing studies. Our response is in italics.

- Preclinical studies to evaluate the lowest dose of methylphenidate in the youngest animals that does not impact adult behavior. Preclinical studies to identify factors that would protect the developing nervous system from methylphenidate's adverse effects. *We agree that the field needs more data on the long-term effects of all psychiatric medications in all populations. However, preclinical postmarketing studies are meant to evaluate a specific safety issue with a specific product. General exploratory preclinical studies are not appropriate. Given the nebulous outcomes of "impacting adult behavior" and "protective factors," there is no specific study that the Division could request from the Applicant.*

- An epidemiological surveillance study to examine the long-term effect of stimulants in humans. *Again, we agree that the field lacks rigorous data regarding the long-term effects of most medications. But absent a specific safety concern with this product, a postmarketing study for Aptensio XR is not appropriate. The Agency may wish to consider a future surveillance study of stimulants in cooperation with the National Institutes of Health, but such a study is beyond the scope of this Application.*

- Evaluation of a lower dosage form of Aptensio XR. *Based on the pharmacokinetic study, preschool children have a greater exposure to Aptensio XR than school-aged children. However, based on the optimized doses preschool children received during RP-BP-EF003, there does not appear to be a need for smaller dosages. It is possible a smaller dosage could be beneficial to preschool children during the titration phase, but, because of the problems with weight loss, the limitation of use will obviate the need for a lower dosage.*

- Evaluation of Aptensio XR versus parent training. *Although the Applicant did not compare Aptensio XR head-to-head with parent training, they included a parent training component in Study RP-BP-EF003. At the end of the parent-training phase, most children were still symptomatic enough to qualify for the medication phases of the study. A head-to-head comparison of Aptensio XR and parent training would be complex (requiring placebo medication and a behavioral intervention to serve as a control for the parent training) and it is unclear how useful such a study might be. Ultimately, with the limitation of use, there is no need for this study.*

In conclusion, we do not recommend any postmarketing studies for this Application.

# 10. Recommended Comments to the Applicant

None.

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