Joint Supervisory Memo

Date	*see electronic date*
From	Bernard Fischer, MD (Cross-Discipline Team Leader) Tiffany R. Farchione, MD (Acting Division Director)
Subject	Joint Supervisory Memo
NDA/BLA # and Supplement#	NDA 212038
Applicant	Purdue Pharma Canada
Date of Submission	04/27/2018
PDUFA Goal Date	02/27/2019
Proprietary Name (code name)	Adhansia XR (PRC-063)
Established or Proper Name	Methylphenidate HCL
Dosage Form(s) and strengths	extended-release capsule: 25, 35, 45, 55, 70, 85 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of attention deficit/hyperactivity disorder (ADHD) in patients 6 years and older
Applicant Proposed Dosing Regimen(s)	Start at 25 mg daily, increase by 10 to 15 mg every 5 days.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s)	*Treatment of attention deficit/hyperactivity disorder (ADHD) in patients 6 years and older*
Recommended Dosing Regimen(s)	*Start at 25 mg daily, increase by 10 to 15 mg every 5 days.*

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
This product will provide a new dosage form of methylphenidate, a CNS stimulant approved and marketed in other formulations, for patients with ADHD. There are benefits of having another efficacious treatment option that can be taken once daily and may be either swallowed whole or sprinkled on food. There are no risks unique to this formulation that would alter the previous benefit-risk assessment established by the Division in the approval of stimulants for the treatment of ADHD.

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%. • It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. • These symptoms cause significant impairment in academic and social functioning during critical years of development unless treated.	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 several products that have demonstrated safety and effectiveness in the treatment of ADHD. • Most of these products contain amphetamine salts or methylphenidate. • More recently approved products contain atomoxetine or guanfacine. • These products display differences in time to therapeutic onset and/or duration of action because of different pharmacokinetic profiles. Some products require more than one dose per day because of a short duration of action. • Products have been developed as different formulations (tablets, capsules,	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or oral suspensions), which allow for different modes of oral administration (sprinkling on food, chewing, swallowing intact pills or capsules).	

Benefit	• Adhansia XR demonstrated statistically significant and clinically meaningful improvement in ADHD symptoms at doses:
	  • 45 and 100 mg for adults (doses 25 and 70 mg were not significant)
	  • 45 and 70 mg for adolescents aged 12 to 17 years (doses 25 and 85 mg were not significant).
	• Adhansia XR demonstrated statistically significant and clinically meaningful improvement in ADHD symptoms at post-dose time-points:
	  • 1, 2, 5, 8, and 11 hours in adults (Hour 14 was not statistically significant, but Hour 16 was)
	  • 1, 2, 4, 6, 8, 10, 12, and 13 hours in children aged 6 to 12 years
		Overall, the submitted studies provide substantial evidence of effectiveness. (b) (4) .

Risk and Risk Management	• Observed adverse reactions were consistent with the simulant drug class. • In adults, adverse reactions appeared to disproportionately increase at doses of (b) (4) mg. • In pediatric patients, adverse reactions appeared to disproportionately increase at doses of 70 mg and higher.	The risks of Adhansia XR can be mitigated through labeling. Dosing recommendations include the following language: Titrate the dose in increments of 10 to 15 mg at intervals of no less than 5 days. Dosages higher than 100 mg daily in adults and 85 mg daily in pediatric patients have not been evaluated in clinical trials and are not recommended. Although efficacy was demonstrated in short-term controlled trials in adults at dosages of 100 mg daily, dosages above 85 mg daily were associated with a disproportionate increase in the incidence of certain adverse reactions. In short-term controlled

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		trials in pediatric patients, efficacy was demonstrated at dosages of 70 mg daily, but dosages of 70 mg daily and higher were associated with a disproportionate increase in the incidence of certain adverse reactions. Individualize dosage adjustments based upon assessment of clinical benefit and tolerability with careful consideration of the dose-related adverse reactions.

2. Background

This application for an extended-release methylphenidate uses the 505(b)(2) pathway and references Ritalin as the listed drug. The drug product is intended for once-daily oral administration in the morning.

In 2013, the Applicant requested a meeting with the Division and expressed interest in developing an extended-release methylphenidate product (b) (4) The target population was adolescents and adults with ADHD. The Division's written response (issued June 14, 2014) advised the Applicant to include studies of children ages 6 to 12 years in the development program because ADHD is a childhood-onset disease and the Division had evidence that this population used long-acting stimulants.

On December 30, 2016, the Division met with the Applicant and advised conducting a fixed-dose study in children 6 to 12 years old and including this age group in their open-label safety study.

The Division of Medication Error Prevention and Analysis (DMEPA) denied the Applicant's initial proprietary name request for (b) (4) DMEPA approved the name "Adhansia" on May 8, 2017.

3. Product Quality

The product quality review was performed by:

- Drug Substance: Sithamalli Chandramouli (primary), Su Tran (secondary)
- Drug Product: Andrei Ponta (primary), Wendy Wilson-Lee (secondary)
- Process/Microbiology, Facility: James Laurenson and Cai Chunsheng (primary), Raanan Bloom and Rapti Madurawe (secondary)
- Biopharmaceutics: Parnali Chatterjee (primary), Ta-Chen Wu (secondary)
- Technical Lead: David Claffey

The drug product is composed of microbeads; 20% of the dose is in an immediate-release layer and 80% of the dose in a (b) (4) extended-release layer (b) (4) Strengths (25, 35, 45, 55, 70, and 85 mg) are based on the methylphenidate hydrochloride salt. At controlled room-temperature, the expiratory date is 24 months.

The drug substance information was referenced from DMF (b) (4) all were found adequate. The manufacturing process is adequately controlled. The dissolution process, (6 hours at pH 1 and 10 hours at pH 7.4) measured at four timepoints, was acceptable. In an in vitro alcohol-induced dose-dumping study, an appreciable increase in the release of methylphenidate was found at alcohol concentration of 40% v/v, but not at 5 to 20% v/v

alcohol concentrations. This information was added to the label. The extended release claim was accepted.

The Quality Review Team recommends 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 drug product uses a (b) (4) methacrylate copolymer (b) (4). Based on the calculations from Dr. Rao, (b) (4) of the drug product (b) (4) offers margins of at least (b) (4) times the no observed adverse effect level (NOAEL) in children, adolescents, and adults, respectively. All other listed excipients are at acceptable levels per the Agency's Inactive Ingredients Database.

The Pharmacology/Toxicology Team recommends approval.

5. Clinical Pharmacology

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

- After administration of Adhansia XR, two distinct peak concentrations are observed with the 1st occurring in about 1.5 hours and the 2nd in about 12 hours post dose. This is indicative of the immediate and delayed release components of the formulation.

- After administration of 100 mg Adhansia XR daily and 20 mg IR methylphenidate three times daily for 5 days in a comparative bioavailability study, exposure to racemic (d,l)-methylphenidate (AUC0-24) and minimum concentration (Cmin) were about 50% and 288% higher after Adhansia XR, respectively. The 1st peak concentration (Cmax) was 22% higher but the 2nd Cmax was similar at steady state. Partial (p) AUC 0-4h, pAUC8-12h, pAUC12-16h, pAUC12-t were about 31%, 13%, 126%, 220% higher, respectively, but AUC4-8h was about 20% lower after Adhansia XR compared to IR methylphenidate at steady state. The exposures were not equivalent except pAUC8-12h. Clinical safety and efficacy studies were thus required to demonstrate effectiveness at various time points during the day up to 16 hours post-dose.

- AUC0-inf and AUC0-t of methylphenidate are equivalent after a single dose administration of 70 mg Adhansia XR and 72 mg Concerta. However, pAUCs (AUC0-3, AUC3-7, AUC7-12, AUC12-16) and Cmax of methylphenidate were not equivalent. Clinical safety and efficacy studies were thus required to demonstrate effectiveness at various time points during the day up to 16 hours post-dose.

- Adhansia XR can be administered with or without food. The entire contents of Adhansia XR capsule can be sprinkled on applesauce or yogurt and consumed without chewing.

- Given that the delayed release coating is dissolved and methylphenidate is released (b) (4) pH modulators, such as proton pump inhibitors, should be co-administered with caution and based on clinical response, with alternate medication used if needed.

The Clinical Pharmacology Team recommends approval.

6. Clinical Microbiology

See Section 3 for the product's Quality Review Team. The microbiology review found that the proposed drug product is a non-sterile capsule. The Applicant performed microbiological tests on release and stability of the drug product. All batches have met USP specifications to date. The Applicant intends to continue monitoring microbiological quality per USP specifications for the commercial product. This is acceptable (p. 9, Quality Assessment for NDA 212038).

7. Clinical/Statistical Efficacy

The primary clinical reviewer was Nancy Dickinson; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Satish Misra; the secondary reviewer was Team Leader Peiling Yang (with assistance from primary biostatistics reviewer Yang (Kelly) Yang). Dr. Peiling Yang and her Division Director, H.M. James Hung, disagreed with many of the analyses and interpretations from Dr. Misra's review. Therefore, Dr. Peiling Yang's biostatistics review forms the basis for the summary below.

Table 1 includes the clinical studies submitted for efficacy for this NDA. The review team used Studies 063-008 and -010 to evaluate effectiveness in adults and Studies 063-009 and -015 to evaluate effectiveness in pediatric patients (ages 12 to less than 18 and ages 6 to less than 12, respectively).

Table 1. Efficacy Studies Submitted for NDA 212038.

Study Identifier	N	Study Design/ Population	Doses evaluated (oral, daily)	Duration of Treatment	Outcome Measure
063-008	59	Randomized Placebo-controlled Cross-over Adults (18 to 58 years)	25 mg 35 mg 45 mg 55 mg 70 mg 85 mg 100 mg	2 to 7 weeks open-label dose-optimization Two, 1 week double-blind periods	PERMP (Adult Workplace Environment)
063-009	354	Randomized Placebo-controlled Adolescents (12 to 17 years)	25 mg 45 mg 70 mg 85 mg	4 weeks fixed-dose	ADHD-5-RS after 4 weeks double-blind
063-010	375	Randomized Placebo-controlled Adults (18 to 72 years)	25 mg 45 mg 70 mg 100 mg	4 weeks fixed-dose	ADHD-5-RS after 4 weeks double-blind
063-015	156	Randomized Parallel-group Children (6 to 12 years)	25 mg 35 mg 45 mg 55 mg 70 mg 85 mg	6 weeks open-label dose-optimization 1week double-blind	SKAMP-C (Laboratory Classroom)

ADHD-5-RS = Attention Deficit Hyperactivity Disorder Rating Scale, DSM-5 Version; PERMP = Permanent Product Measure of Performance; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn and Pelham- Combined score.

Study 063-008 (adults)

After a 2- to 7-week dose optimization phase, patients were randomized to either 1 week of drug followed by 1 week of placebo or the reverse. At the end of each randomized, double-blind week, patients completed a testing day in an Adult Workplace Environment. On testing days, the Permanent Product Measure of Performance (PERMP) was collected pre-dose and at 1, 2, 5, 8, 11, 14, and 16 hours post-dose (see Table 2 for results). Prespecified secondary endpoints were the first time that the drug statistically separated from placebo (the Applicant called this "onset of effect") and the last time the drug separated from placebo (the Applicant called this "duration of effect").

Table 2. PERMP Results at Each Time Point for Study 063-008.

Post-dose Time	0.0h[b]	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Diff[a] (SE)	-10.96 (6.448)	18.37 (6.388)	17.52 (6.378)	11.93 (6.620)	19.30 (5.667)	20.38 (8.946)	8.36 (7.078)	19.56 (6.521)
95% CI	(-23.97, 2.04)	(5.49, 31.25)	(4.66, 30.38)	(-1.42, 25.28)	(7.87, 30.72)	(2.33, 38.42)	(-5.92, 22.63)	(6.40, 32.71)
p-value	0.0963	0.0063	0.0088	0.0786	0.0014	0.0278	0.2442	0.0045

LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean at a given hour.
[b] pre-dose.
Note: Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model for all subjects includes terms for treatment, period, sequence, time, and treatment-by-time. P-values were not adjusted for multiplicity.
[Source: Table 6 of Applicant CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

The results showed efficacy at hours 1, 2, 8, 11, and 16 hours—but not at Hours 5 and 14. The Applicant noted that there was large period effect (whether the patient took drug or placebo first in the cross-over phase of the study), especially in the pre-dose scores. They conducted two post-hoc analyses:

- The pre-dose score was changed from a dependent variable to a covariate in their model (Table 3)
- The dependent variable was changed from the score at each time point to the change from the pre-dose score (Table 4)

Table 3. PERMP Results at Each Time Point for Study 063-008; Applicant's First Post-hoc Analysis.

	Treatment Difference (PRC-063 – Placebo) in **Post-dose PERMP-T Score**						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Diff[a] (SE)	27.86 (5.595)	27.60 (5.932)	22.36 (7.060)	30.09 (6.112)	31.32 (9.390)	18.01 (9.836)	30.38 (8.446)
95% CI	(16.57, 39.14)	(15.64, 39.56)	(8.12, 36.60)	(17.76, 42.41)	(12.39, 50.26)	(-1.83, 37.84)	(13.35, 47.41)
Treatment p-value	<0.0001	<0.0001	0.0028	<0.0001	0.0018	0.0741	0.0008

LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean at a given hour.
Note: Analyses utilize repeated measures mixed-effects analysis of covariance models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and interaction and pre-dose score as a covariate.
[Source: Table 9 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 4. PERMP Results at Each Time Point for Study 063-008; Applicant's Second Post-hoc Analysis.

	Treatment Difference in **Change from Pre-dose PERMP-T Score**						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Diff[a]	28.35	27.37	22.17	29.86	30.58	18.08	29.22
(SE)	(5.744)	(5.905)	(7.033)	(6.126)	(9.369)	(9.746)	(8.238)
95% CI	(16.77, 39.93)	(15.46, 39.28)	(7.99, 36.36)	(17.50, 42.21)	(11.69, 49.48)	(-1.57, 37.74)	(12.60, 45.83)
Treatment p-value	<0.0001	<0.0001	0.0030	<0.0001	0.0022	0.0704	0.0010

LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean at a given hour.
Note: Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and treatment-by-time interaction.
[Source: Table 10 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

These changes led to statistical significance for the Hour 5 time-point, but the Hour 14 time-point remained non-significant. Dr. Peiling Yang agreed that these post-hoc adjustments were appropriate.

Study 063-009 (adolescents)
Data from Site 8 (10 completers, 3 early terminations) was excluded from analysis after the Applicant's for-cause inspection (due to poor source documentation) discovered numerous protocol and Good Clinical Practice violations. The Agency's sensitivity analysis demonstrated that excluding this site had no effect on the determination of efficacy.

The Applicant amended the statistical analysis plan (SAP) for this study twice without presenting these changes to the Agency. Their NDA submission, which compared pooled drug versus placebo and used last-observation-carried-forward, was not acceptable. Therefore, the biostatistics team conducted their own analysis of the data using the last SAP the Agency had agreed upon (Table 5).

Table 5. Agency Calculation of Study 063-009 Results.

Treatment Group	n	Primary Efficacy Measure: Change from Baseline (Week 1, Visit 2) in ADHD-5-RS Total Score to Week 5 (Visit 6)				
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)	Unadjusted p-value	Adjusted p-value
25 mg	71	37.7 (8.69)	-12.77 (1.35)	-2.18 (-5.94, 1.59)	0.2562	0.5297
45 mg*	68	36.4 (8.52)	-16.03 (1.39)	-5.44 (-9.25, -1.63)	0.0052	0.0170
70 mg*	72	35.9 (8.42)	-15.79 (1.35)	-5.20 (-8.95, -1.44)	0.0069	0.0224
85 mg	70	37.8 (8.13)	-15.03 (1.39)	-4.43 (-8.24, -0.63)	0.0226	0.0692
Placebo	71	37.3 (8.40)	-10.59 (1.35)	--	--	--

n: number of subjects in the full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses that are statistically significantly different from placebo after adjusting for multiplicity.
[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA prior to trial completion.]

Study 063-010 (adults)

The Applicant also amended the SAP for this study without presenting the changes to the Agency. The Agency biostatistics team's analysis of the data is presented in Table 6.

Table 6. Agency Calculation of Study 063-010 Results.

Treatment Group	Primary Efficacy Measure: Change from Baseline (Week 1) in ADHD-5-RS Total Score to Week 5					
	n	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)	Unadjusted p-value	Adjusted p-value
25 mg	75	36.1 (8.14)	-11.63 (1.31)	-1.93 (-5.59, 1.74)	0.3016	0.5919
45 mg*	73	36.5 (7.19)	-16.83 (1.34)	-7.12 (-10.82, -3.43)	0.0002	0.0006
70 mg	71	35.4 (7.44)	-12.00 (1.37)	-2.29 (-6.04, 1.45)	0.2287	0.4889
100 mg*	72	37.0 (7.94)	-17.57 (1.39)	-7.86 (-11.63, -4.09)	<0.0001	0.0003
Placebo	77	35.7 (8.42)	-9.71 (1.32)	--	--	--

n: number of subjects in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses that are statistically significantly different from placebo after adjusting for multiplicity.
[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA]

Study 063-015 (children)

After a 6-week dose optimization phase, patients were randomized to 1 week of drug at the optimized dose or placebo (see Table 7 for the distribution of optimized doses).

Table 7. Optimized Dose Distribution for Study 063-015.

	Optimal PRC-063 Dose						Total PRC-063	Total Placebo	Total Subjects
	25 mg	35 mg	45 mg	55 mg	70 mg	85 mg			
Randomized	9	15	20	19	8	4	75	73	148
Completed*	8	15	20	19	8	4	74	73	147

*Completed study to the full day laboratory classroom
[Source: Table 3 of Applicant's CSR]

At the end of the randomized, double-blind week, patients completed a testing day in a laboratory classroom environment. On the testing day, the Swanson, Kotkin, Agler, M-Flynn and Pelham-Combined (SKAMP-C) score was collected pre-dose and at 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose. The primary endpoint was the post-dose SKAMP-C score averaged for all doses and timepoints (Table 8). The prespecified secondary endpoints were the post-dose SKAMP-C scores averaged across doses for each time point (Table 9).

Table 8. Primary Endpoint, Study 063-015.

Treatment Group	Mean Pre-Dose Score on Classroom Day (SD)	LS Mean (SE) for the Classroom day	Placebo-subtracted Difference[a] (95% CI)
PRC-063 (N=74)	14.4 (10.58)	10.3 (0.74)	-8.6 (-10.6, -6.6)
Placebo (N=73)	11.5 (7.13)	18.9 (0.73)	--

N: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a]Least-Squares Mean Difference (drug minus placebo).
Larger scores represent more severe symptoms.
[Source: Table 14.2.1.1.1 and Table 14.2.1.1.4 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 9. Secondary Endpoints, Study 063-015.

Post-Dose Hour	PRC-063 [N=74] LS Means (SE)	Placebo [N=73] LS Means (SE)	LS Mean Difference[a] (SE)	95% CI	p-value
hour 1	8.8 (0.98)	17.6 (0.97)	-8.8 (1.36)	(-11.5, -6.1)	< 0.0001
hour 2	10.1 (0.90)	20.1 (0.89)	-10.1 (1.25)	(-12.5, -7.6)	< 0.0001
hour 4	11.5 (0.94)	19.9 (0.93)	-8.4 (1.31)	(-11.0, -5.9)	< 0.0001
hour 6	11.1 (0.93)	20.1 (0.92)	-9.0 (1.30)	(-11.6, -6.4)	< 0.0001
hour 8	11.7 (0.97)	20.9 (0.96)	-9.1 (1.35)	(-11.8, -6.5)	< 0.0001
hour 10	9.9 (0.98)	18.8 (0.97)	-8.9 (1.37)	(-11.6, -6.2)	< 0.0001
hour 12	9.9 (0.91)	16.7 (0.90)	-6.8 (1.26)	(-9.3, -4.3)	< 0.0001
hour 13	9.6 (0.99)	16.9 (0.98)	-7.3 (1.38)	(-10.1, -4.6)	< 0.0001

CI = confidence interval; LS = least squares; SE = standard error; p-values are not adjusted for multiplicity.
[a]Least-Squares Mean Difference (drug minus placebo).
[Source: Table 9 and 10 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Efficacy Summary

Exploratory subgroup analyses found no indication of differential effects in males versus females, whites versus non-whites, or U.S. versus Canadian patients.

Summaries of the statistically significant results by dose and by time are presented in Table 10 and Table 11, respectively.

Table 10. Statistically Significant Results by Dose Across Applicant's Fixed-dose Studies.

Study	Population	Significance at Fixed Dose			
		25 mg	45 mg	70 mg	Highest Dose 85 mg Adolescents 100 mg Adults
063-009	Adolescents (12 to 17 years)	No	Yes	Yes	No (85 mg)
063-010	Adults	No	Yes	No	Yes (100 mg)

Table 11. Statistically Significant Results by Time Across Applicant's Dose-optimization Studies.

Study	Population	Significance at Time Points											
		1	2	4	5	6	8	10	11	12	13	14	16
063-015	Pediatric (6 to 12 years)	Yes	Yes	Yes	-	Yes	Yes	Yes	-	Yes	Yes	-	-
063-008	Adults	Yes	Yes	-	Yes[a]	-	Yes	-	Yes	-	-	**No**	Yes

- = Not tested.
[a]Significant based on post-hoc adjustments as previously described.

Taken together, the data from studies in adults and in children as young as 6, including the bridging studies to the listed drug as well as the clinical trials with this novel formulation, constitute substantial evidence of effectiveness; therefore, we recommend approval. However, the unique pattern of significant results (no clear dose-response and time periods of inefficacy preceded and followed by periods of efficacy) presented unique challenges to labeling (see Section 12).

8. Safety

The primary clinical reviewer was Nancy Dickinson; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer. As discussed by Dr. Dickinson in her review, a dose-optimization period prior to randomization makes it difficult to determine 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. There were no perturbations in vital signs demonstrating a unique safety signal for this stimulant formulation. There were no clinically significant abnormal laboratory values.

Study 063-008 (adults)
During Study 063-008 (dose-optimization followed by a double-blind cross-over study), 10% of Adhansia XR-treated patients discontinued due to adverse reactions compared to 0% of placebo-treated patients. The following adverse reactions led to discontinuation at a frequency of ≥ 2% of Adhansia XR-treated patients: nausea, bronchitis, gastroenteritis viral, viral infection, blood pressure increased, and hypomania.

Study 063-009 (adults)
Adverse events from Study 063-009 (fixed-dose study) are presented in Table 12.

Study 063-010 (adolescents)
Adverse events from Study 063-010 (ages 12 to 17 years, fixed-dose study) are presented in Table 13. Two adolescent patients taking Adhansia XR, 70 and 85 mg, had delirium leading to discontinuation.

Table 12. Adverse Events Occurring in ≥2% Adult Patients on Adhansia XR versus Placebo, Study 063-009.

Adverse Reaction	Adhansia XR				All doses Adhansia XR (n=297)	Placebo (n=78)
	25 mg (n=77)	45 mg (n=73)	70 mg (n=73)	100 mg (n=100)		
Initial Insomnia	4%	8%	6%	7%	5%	1%
Insomnia	17%	11%	16%	19%	13%	4%
Dry mouth	8%	8%	7%	14%	8%	4%
Nausea	4%	6%	4%	11%	5%	3%
Diarrhea	1%	3%	7%	5%	3%	1%
Decreased appetite	4%	7%	15%	19%	9%	3%
Feeling jittery	1%	3%	8%	4%	4%	1%
Weight decreased	3%	4%	3%	5%	3%	1%
Upper respiratory tract infection	0%	4%	3%	3%	2%	1%

Table 13. Adverse Events Occurring in ≥2% Adolescent Patients on Adhansia XR versus Placebo, Study 063-010.

Adverse Reaction	Adhansia XR				All doses Adhansia XR (n=293)	Placebo (n=74)
	25 mg (n=73)	45 mg (n=72)	70 mg (n=76)	85 mg (n=72)		
Decreased appetite	7%	19%	28%	26%	20%	0%
Insomnia	4%	0%	9%	13%	6%	1%
Initial Insomnia	4%	7%	5%	4%	5%	1%
Weight decreased	1%	3%	8%	13%	7%	0%
Abdominal pain upper	5%	1%	5%	4%	4%	1%
Nausea	3%	6%	7%	8%	6%	4%
Dizziness	3%	0%	4%	4%	3%	0%
Dry mouth	1%	0%	5%	4%	3%	1%
Vomiting	1%	1%	3%	6%	3%	0%

Study 063-015 (children)

During the open-label treatment phase of Study 063-015 (ages 6 to 12 years, dose-optimization followed by randomized, placebo-controlled, double-blind study), adverse reactions reported in > 5% of patients included: decreased appetite (35%), upper abdominal pain (15%), affect lability (13%), nausea or vomiting (13%), weight decreased (12%), insomnia (10%), irritability (10%), headache (10%), and heart rate increased (5%).

Safety Summary
In Study 063-009, there was no obvious dose-response for most AEs. However, in Study 063-009, dry mouth and nausea increased disproportionately in the 100 mg-group while decreased appetite increased disproportionately in the 70- and 100-mg-groups.

In Study 063-010, weight loss, decreased appetite, insomnia, and vomiting appeared to demonstrate at least a partial dose-response. Coupled with the two incidents of delirium (one at 70 mg and one at 85 mg), it appeared that a disproportionate increase of AEs (in total) was seen at and above 70 mg.

There were no unique, unexpected safety signals identified in the Adhansia XR development program. All of the reported AEs were consistent with our prior experience with the stimulant class and can be mitigated through labeling.

9. Advisory Committee Meeting

This section is not applicable to this application.

10. Pediatrics

See Sections 7 and 8 for a review of the effectiveness and safety in pediatric patients.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Division of Medication Error Prevention and Analysis (DMEPA)
Loretta Holmes, DMEPA reviewer, and Teresa McMillan, DMEPA Team Leader, reviewed the Applicant's proposed labeling and packaging. DMEPA found the labeling and packaging acceptable.

Division of Pediatric and Maternal Health (DPMH)
The primary DPMH reviewer was Carrie Ceresa, the secondary reviewer was Team Leader Miriam Dinatale. DPMH revised subsections 8.1, 8.2, and 17 in the Adhansia XR label for compliance with the PLLR.

Controlled Substance Staff (CSS)
The primary CSS reviewer was Shalini Bansil, the secondary reviewers were Team Leader Martin Rusinowitz and senior pharmacologist Silvia Calderon. The CSS review states that Adhansia XR is expected to have similar abuse liability as other MPH products given its similar relative bioavailability when compared to immediate-release methylphenidate as well

as its similar adverse event profile. The CSS Team concurs with the Applicant that Adhansia should be maintained on Schedule II of the Controlled Substances Act.

Dosing, Safety, and Efficacy

Because of the timing of statistical significance in Study 063-008, (b) (4) Although Hour 16 was positive, Hour 14 was not. (b) (4)

There was no clear efficacy-related dose-response—and the highest doses tested were not statistically different from placebo. However, considering the totality of the results, the Division believes that efficacy was demonstrated for Adhansia XR. Because of the pattern of efficacy results and reported adverse reactions, the Division included the following dosing recommendation in the label:

> Titrate the dose in increments of 10 to 15 mg at intervals of no less than 5 days. Dosages higher than 100 mg daily in adults and 85 mg daily in pediatric patients have not been evaluated in clinical trials and are not recommended. Although efficacy was demonstrated in short-term controlled trials in adults at dosages of 100 mg daily, dosages above 85 mg daily were associated with a disproportionate increase in the incidence of certain adverse reactions. In short-term controlled trials in pediatric patients, efficacy was demonstrated at dosages of 70 mg daily, but dosages 70 mg daily and higher were associated with a disproportionate increase in the incidence of certain adverse reactions. Individualize dosage adjustments based upon assessment of clinical benefit and tolerability with careful consideration of the dose-related adverse reactions.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There was no unique safety signal identified for this product that would require a REMS.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Division will require two PMCs:

1. PMC 3570-1, Conduct an open-label, randomized, multiple-dose, safety, tolerability, and pharmacokinetic study of Adhansia XR (methylphenidate extended-release tablets) in male and female children (4- to less-than-6-years of age) with ADHD. The Sponsor proposes to extrapolate efficacy using the PK data in children 4-5 years of age.
Final protocol submission: 08/2019
Study Completion: 08/2021
Final report submission: 02/2022

2. PMC 3570-2, Conduct a 1-year, open-label extension study to obtain additional information on safety and tolerability of Adhansia XR (methylphenidate extended-release tablets) in children ages 4 to 12 years diagnosed with ADHD.
Final protocol submission: 08/2019
Study Completion: 03/2024
Final report submission: 09/2024

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
02/27/2019 06:39:34 PM
Acting Lead Medical Officer

TIFFANY R FARCHIONE
02/27/2019 06:41:07 PM