CLINICAL REVIEW

Application Type	Class 1 NDA resubmission
Application Number(s)	209311
Priority or Standard	Priority
Submit Date(s)	June 8, 2018
Received Date(s)	June 8, 2018
PDUFA Goal Date	August 8, 2018
Division / Office	Division of Psychiatry Products/ ODE 1
Reviewer Name(s)	Nancy Dickinson, PharmD.
Review Completion Date	August 7, 2018
Established Name	Methylphenidate hydrochloride
Code Name	HLD200
(Proposed) Trade Name	Jornay PM
Therapeutic Class	Psychostimulant
Applicant	Ironshore
Formulation(s)	Extended Release
Dosing Regimen	20, 40, 60, 80, or 100 mg taken once daily in the evening
Indication(s)	Treatment of ADHD
Intended Population(s)	Pediatric patients ages 6 and above

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Tables- (All tables reviewer created from Applicant datasets)

Background

HLD200, tradename Jornay PM, contains methylphenidate, a known psychostimulant for the treatment of Attention Deficit and Hyperactivity Disorder (ADHD). The proposed doses are 20, 40, 60, 80, and 100 mg once daily in the evening, prior to sleep. Initial dosing for 6 years and older is 20 mg at 8:00 p.m. The release mechanism is formulated for drug release upon awakening to improve ADHD symptoms that impair functioning while preparing for school.

The HLD200 formulation is a delayed-release and extended-release (ER) coated core that allows for release of methylphenidate in plasma at a controlled rate following an initial delay of approximately 6 to 8 hours. No more than five percent of total drug is available within the first 10 hours after dosing. After the lag period, the absorption of methylphenidate occurs in a single peak at approximately 14 hours post-dosing (mean T_{max} = 13 hours). The half-life of methylphenidate in adults following oral administration of HLD200 was approximately 6 hours.

The purpose of this Class 1 NDA resubmission is to seek approval of HLD200 for treatment of ADHD with an accurate label (package insert).

Recommendation

I recommend approval of HLD200 for treatment of ADHD in pediatric patient 6 years and above. After review of HLD200's (NDA 209311) regulatory history, proposed package insert, safety data from the original NDA, and secondary endpoint information, the drug application meets substantial evidence of effectiveness and safety for approval. The package insert, which was pending from the original NDA review cycle, is agreed to with the Applicant.

ADHD is a childhood-onset disease with core symptoms of inattentiveness and/or hyperactivity. Psychostimulants or Central Nervous System (CNS) stimulants, have been the mainstay of pharmacologic therapy for ADHD for a half-century. Methylphenidate (reference listed drug Ritalin) is a psychostimulant. It was reformulated multiple times since the 1990s to increase the duration of clinical effect to address ADHD symptoms during the school day as well as evening activities. The HLD200 formulation is designed to affect clinical functioning upon morning awakening without awaiting time to drug onset with medication dosed in the morning. Yet, the timing of the clinical effect must be balanced with not awakening too early or causing insomnia prior to bedtime because the drug has not yet been eliminated at the end of the day.

HLD200 is effective based two clinical trials in patients (6 to 12 years) with ADHD, any subtype (Studies 107 and 108). The two trials have different, but complementary, primary and secondary endpoints—both showing statistically significant improvement in ADHD manifestations compared to placebo.

The difference in the two efficacy trial designs can account for the vast difference in incidence of insomnia and other stimulant-related, expected adverse events reported during the double-blind treatment phases. The trial designs are described in the Section on Pivotal Clinical Trials.

Overall, the safety issue of insomnia, identified during the original NDA review cycle, does not preclude approval of HLD200. Although substantial reports (40%+) of insomnia occurred from the time of drug initiation lasting at least 2 weeks, no patients discontinued the trials specifically due to insomnia. The difference in trial designs, namely absence of an open-label lead-in phase in Study 108, made HLD200 in this study appear worse than in Study 107 during the placebo-controlled, double-blind phase.

Regulatory History

This New Drug Application (NDA) review is for a Class 1 resubmission of HLD200, an extended-release methylphenidate submitted on June 8, 2018. The original NDA 209311 for HLD200 was submitted September 30, 2016, under 505(b)(2). Ritalin (methylphenidate) is the reference listed drug. The original application received a Complete Response action on July 28, 2017, due to the safety issue of 33% rate of insomnia in Study 108.

The Applicant, Ironshore, submitted a formal dispute resolution request on March 27, 2018. Meeting minutes from the dispute resolution, dated May 21, 2018, discuss four issues:

1. Insomnia for HLD200 can be described in the label and is not unique to HLD200 among psychostimulants.
2. Cross-study comparison of rates of insomnia between Studies 107 and 108 did not account for the different study designs.
3. Pharmacokinetic data of methylphenidate blood levels at 6 hours post-dose are barely detectable. Clinically significant levels are detectable at 8 to 10 hours post-dose indicating HLD200 is not being released early (overnight).
4. The key secondary endpoints used for the labeling claims of improved early morning functioning.

On May 21, 2018, the Applicant received an Appeal Granted letter signed by the Office of Drug Evaluation 1 Deputy Director, Dr. Robert Temple. The letter indicated:

- Agreement with Ironshore that the risk of insomnia with HLD200 was overestimated in Study 108 and is an artifact of the study design.
- The outstanding issue of improvement of early morning functioning will be further considered during labeling discussions after NDA resubmission.

Subsequently, on June 8, 2018, Ironshore resubmitted their NDA 209311 as a Class 1 resubmission.

Review strategy

Based upon the regulatory history of this application, the outstanding issues are:

1. Safety review
2. Package Insert labeling, including the Section 2.2: Dosing an Administration, Section 6.1: Adverse Reactions, Clinical Trial Experience and Section 14: Clinical Studies description
3. Addition of (b) (4) in the label, as assessed (b) (4)

This review is my analysis of information and data from the following sources:

- Applicant's proposed label in the June 8, 2018, resubmission
- Division of Psychiatry's proposed label sent to Applicant during original NDA cycle, July 2017
- Safety datasets and subject level datasets from pivotal Phase 3 trials, Study 107 and Study 108 in the original NDA application analyzed using JMP 11.0 and JMP Clinical 6.0

Notably, the September 30, 2016, NDA application contained an Integrated Summary of Safety (ISS) dataset containing Study 106 and 107, both with the same study design. This review does not discuss safety findings from Study 106 because the drug formulation was not the to-be-marketed one and therefore Study 106 was not considered to be a pivotal trial. The safety results of Study 106 align with adverse events reported in Study 107.

Pivotal Clinical Trials

Study 107 (Pivotal study #1)

Design:

Study HLD200-107 was a 7-week, Phase 3 trial. The randomized withdrawal trial was designed with a 6-week open-label dose optimization phase, followed by a 1-week, double-blind, randomized treatment phase of HLD200 (20, 40, 60, 80, and 100 mg) or

placebo. The mean dose was 50 ± 15 mg/day; only four patients received the 100 mg/day dose.

Subjects:

Study 107 enrolled 161 pediatric patients (6 to 12 years) diagnosed with ADHD. The package insert will list the Intent-to-Treat (ITT) population as 117 and the safety population as 119. Refer to Dr. Glenn Mannheim's clinical review of the original NDA, dated July 24, 2017, for subject demographic information.

The multicenter study was conducted at seven centers. The data integrity at two centers, #15 and #10, was questioned based on the Applicant's evaluation of data integrity submitted August 15, 2016. The Office of Scientific Investigations (OSI) was consulted.

Clinical site #15 had a compliance violation where multiple shipments were made for HLD200 (but no placebo) as described in Ironshore's Note-to-File dated December 2, 2015. This led to the site submitting multiple randomization requests for each subject until the subject was assigned to HLD200. Eventually, the error was remedied and, according to the Study 107 ADAM Subject Level (ADSL) dataset, subjects at that site were randomized to either placebo or HLD200 and both study medications were dispensed to the subjects. We concluded that the non-compliance error did not impact data integrity, thus included subjects from site #15 in the analysis. Refer to the Office of Scientific Inspection's (OSI) Clinical Inspection Summary dated July 6, 2017.

Clinical site #10 (n=36), is removed from the ITT and safety populations in the package insert because of lack of data integrity. On May 3, 2016, Ironshore submitted general correspondence about outlier data with site #10. The unlocked data revealed the same vital signs for multiple patients at different time points and the primary endpoint scores did not show the expected variability observed at other sites. Refer to Dr. Jasmine Gatti's cross-discipline team leader review dated July 25, 2017. Ironshore also agrees with the removal of data from site #10.

Endpoints:

The ITT population was 117 subjects, HLD200 n=64 and placebo n=53. The primary endpoint was the classroom evaluation study after one week after randomization using the, the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), a 13-item teacher-rated scale that assesses symptoms of ADHD in a classroom setting. The primary efficacy endpoint was the model-adjusted average of all post-dose SKAMP score of combined ADHD subtypes as measured during the 12-hour analog testing period from 8:00 a.m. to 8:00 p.m. Patients taking HLD200 scored was statistically significantly better (lower) on the SKAMP instrument compared to placebo. The SKAMP score mean difference between HLD200 and placebo was -5.9 (confidence interval [-9.1, -2.7]).

The secondary endpoints proposed in the package insert by the Applicant were the PREMB-R AM, a subscale of the Parent Rating of Evening and Morning Behavior - Revised (PREMB-R), (b) (4) The Clinical Outcomes Assessment (COA) Staff initially disagreed with this instrument because the Applicant used the morning subscale without adequate validation to claim improved early morning functioning. Refer to Dr. Wen-Hung Chen's review dated May, 28, 2017.

The PREMB-R AM consists of three questions. Question #1 asks parents how much difficulty the child had getting up and out of bed in the morning. If the patient was randomized to placebo instead of methylphenidate, a psychostimulant, the weight of scoring on the scale on Question #1 (of three questions) could be misleading. Additionally, Question #1 appears less applicable to patients with ADHD compared to the other two functional questions. During the resubmission NDA cycle, we issued an information request to Ironshore for a factor analysis to assess if the question about getting up in the morning was responsible for statistical significance of the secondary endpoint.

In the response to our information request, dated July 16, 2018, the Applicant listed the individual scores and p-values for the three questions on the PREMB-R AM. The patients randomized to HLD200 scored statistically significantly better than placebo on all three questions in Study 107. The factor analysis results were convincing that there was an improvement in early morning functioning for those patients taking HLD200. The Clinical Trials section 14 of the package insert lists the PREMB-R AM, (b) (4) as a positive secondary endpoint as a measure of improvement of early morning functioning.

Safety Population:

The safety population in Study 107 includes 125 patients. After the 6-week, open-label HLD200 dose-optimization period, the patients were randomized to HLD200 (N=65) or placebo (N=54) for 1 week.

There were no serious adverse events or deaths in Study 107.

Patient disposition:

During the open-label treatment phase, seven patients discontinued the trial. Table 1 describes reported adverse events and reasons for discontinuation. I conclude that adverse events, including feeling abnormal, increased diastolic blood pressure, and affect lability from HLD200 lead to the seven patients not completing the study.

My analysis does not match the Applicant's proposed labeling, dated June 8, 2018, (b) (4) Furthermore, the Applicant lists three cases (Subject IDs (b) (6)) in the case report

forms section of the original application which are on Table 1 as discontinuing due to treatment emergent or worsening adverse events. The revised label includes these discontinuations.

No subject discontinued during the randomized, double-blind, placebo-controlled period because of treatment emergent adverse events.

Table 1: Summarized narratives for Non-completers from Study 107

Patient ID (n= 7)	Non-completers: Reason for discontinuing 107 in open-label	Day of D/C	AETERM	AECODE (study day of report)	Related per Investigator	Applicant's CFR
HLD200 (b) (6)	TREATMENT EMERGENT OR WORSENING ADVERSE EVENT	D/C Day 7 due to affect liability			Y	X
HLD200			EMOTIONAL LABILITY	Affect lability (day 1)		
HLD200			HEADACHE	Headache		
HLD200	OTHER	D/C Day 29 due to lack of efficacy				
HLD200			EMOTIONAL LABILITY	Affect lability (day 2)	Y	
HLD200			INCREASED SEVERITY OF INSOMNIA	Insomnia (day 15)	Y	
HLD200			INTERMITTENT UPPER ABDOMINAL PAIN	Abdominal pain upper (day 3)	Y	
HLD200			UPPER RESPIRATORY INFECTION	Upper respiratory tract infection	N	
HLD200	LOST TO FOLLOW-UP	Day 48 lost to follow up; randomized to placebo				
HLD200			EMOTIONAL LABILITY	Affect lability (day 18; taking HLD200)	Y	
HLD200			Early Morning awakening	Terminal insomnia (day 19)	Y	
HLD200	TREATMENT EMERGENT OR WORSENING ADVERSE EVENT	Day 36 due to anxiety and 2 panic attacks				X
HLD200			ANXIETY	Anxiety (day 31)	Y	
HLD200			PANIC ATTACK (two times)	Panic attack (day 31, 32)	Y	
HLD200			WAKING EARLY	Terminal insomnia (day 23)	Y	
HLD200	FAILURE TO CONTINUE TO MEET ALL INCLUSION/EXCLUSION CRITERIA	Day 45 due to failure to meet randomization criteria				
HLD200			INCREASE IN DIASTOLIC BLOOD PRESSURE	Blood pressure diastolic increased (day 23)	N	
HLD200			MOODINESS	Affect lability (day 18)	Y	
HLD200			TIC BEHAVIORS (CHEWING)	Tic (day 38)	Y	
HLD200	TREATMENT EMERGENT OR WORSENING ADVERSE EVENT	Day 22 due to agita ion/aggression				X
HLD200			AGITATION/ AGGRESSION	Aggression (day 5)	Y	
HLD200			AGITATION/ AGGRESSION	Agitation (day 5)	Y	
HLD200			ELEVATED BLOOD PRESSURE - DIASTOLIC	Blood pressure diastolic increased (day 15)	N	
HLD200			ENURESIS (2 times)	Enuresis (day 5, 6)	N	
HLD200			TROUBLE FALLING ASLEEP	Ini ial insomnia (day 6)	Y	
HLD200	SUBJECT OR PARENT/LEGAL GUARDIAN REQUEST	Day 8 due to parent request	SPACEY	Feeling abnormal (day 2)	Y	

Treatment Emergent Adverse Events:

During the open-label treatment phase of Study 107, treatment-emergent adverse events (TEAEs) reported over > 5% included insomnia (41%), decreased appetite (27%), affect lability (22%), headache (18%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%).

The study design of 6-week, open-label, dose optimization treatment phase, allowed patients to acclimate to methylphenidate TEAEs, such as insomnia or affect lability. If the TEAEs were not tolerated, the patients dropped out of the trial by the 1-week, double-blind phase. Thus, the incidence of TEAEs during the placebo-controlled phase of the study was minimal compared to the lead-in phase. There was not a statistical difference in reported TEAEs between the HLD200 and placebo arms. Table 2 lists the adverse events over 5%.

Table 2: Treatment Emergent Adverse Events during double-blind phase- Study 107

Body Organ System	Adverse Event	HLD200 n=65	Placebo n=54
Psychiatric disorders	Any insomnia	5 (8%)	5 (7%)
	Initial Insomnia	4 (6%)	4 (7%)
Investigations	Blood pressure diastolic increased	9 (14%)	7 (13%)

Study 108 (Pivotal study #2)

Design:

Study HLD200-108, the second pivotal Phase 3 trial, has a different study design than Study 107. Study 108 was a 3-week, fixed-dose (40mg, 60mg, or 80mg), double-blind, randomized, placebo-controlled trial conducted at 21 centers. All patients started on 40 mg/day; the mean dose was 52 ± 8 mg/day.

Subjects:

Study 108 enrolled 161 ADHD patients (6 to 12 years). All subjects were included in the efficacy (ITT) and the safety database. (HLD200- N=81; placebo- N=80.)

Endpoints:

The primary endpoint was the ADHD Rating Scale, DSM-IV version (ADHD-RS-IV) Total Score at Visit 5. The ADHD Rating Scale is an 18-question scale with nine questions for each ADHD subtype, inattentive and hyperactive. The mean difference in ADHD-RS-IV Total Scores between HLD200 and placebo was -7.0 (confidence interval [-11.4, -2.7]). The difference was statistically significant between treatment groups, favoring the treatment arm.

The secondary endpoint was the Before School Functioning Questionnaire (BSFQ), a clinician-rated 20-item questionnaire assessing ADHD symptomatology and functioning between 6:00 a.m. and 9:00 a.m. on a severity scale of 0 to 3. Possible scores range from 0 (no difficulty) to 60 (severe difficulty). BSFQ assesses early morning before school activities from the time the child awakens until arrival at school (i.e., early morning routine activities include following directions, breakfast, hygiene, time awareness, getting to school, etc.) and some behaviors not specific to early morning (e.g., talkative, interrupting).

Because the BSFQ was a new instrument to evaluate early morning functioning, COA Staff conducted a review of the scale. Refer to Dr. Wen-Hung Chen's review dated May 28, 2017. Some behaviors measured are not specific to ADHD functioning in the morning such as silliness, blurting out, or being talkative. Therefore, as with study 107, we issued an information request, dated July 16, 2018, to the Applicant for a factor analysis of parents' answers to the 20 questions. Our review of the factor analysis showed that no particular cluster of questions was driving the positive scores of the BSFQ in favor of HLD200. We agreed that the scale did indicate improvement with early morning functioning in the treatment arm and decided to describe the secondary endpoint in the clinical trials section of the package insert.

(b) (4)

Refer to Dr. Glenn Mannheim's clinical review of the original NDA, dated July 24, 2017, for details on the statistically significant efficacy of HLD200 over placebo on the primary endpoints.

Safety Population:

Study 108 contained 161 patients in the safety population. HLD200 n=81 and placebo n=80.

There were no serious adverse events or deaths in Study 108.

Patient Disposition:

In Study 108, 24 randomized subjects discontinued. There were eight discontinuations in the HLD200 arm and 16 assigned to placebo. The reasons for discontinuing the study are investigator decision (unspecified), lost to follow up, other, parent request, and TEAE or worsening adverse event. In the HLD200 arm, one patient (ID (b) (6)) discontinued due to worsening mood swings. In the placebo arm, the worsening adverse events were irritability in two patients, sleep-related adverse events in one patient, and enuresis and vomiting in one patient. Table 3 describes the reasons for discontinuation by treatment group.

Table 3: Reason for Discontinuation - Study 108

Termination Reason	Treatment Arm	
	HLD200	PLACEBO
INVESTIGATOR DECISION	1	0
LOST TO FOLLOW-UP	3	2
OTHER	3	4
SUBJECT OR PARENT/LEGAL GUARDIAN REQUEST	0	6
TREATMENT EMERGENT OR WORSENING ADVERSE EVENT	1	4

Treatment Emergent Adverse Events:

As expected with methylphenidate, the following adverse events occurred at an incidence of ≥ 5% and at a rate at least twice placebo: insomnia (initial, middle, and terminal), decreased appetite, headache, nausea, vomiting, psychomotor hyperactivity, and affect lability or mood swings. Some patients reported both “insomnia” and “(insert timeframe) insomnia” (e.g., terminal insomnia); those adverse events were counted as one in the “any insomnia” total. Table 4 provides the incidence of HLD200-related adverse events reported in Study 108 (incidence of 2% or more and at least twice placebo).

Table 4: Table of Adverse Events Occurring over 2% in HLD200 patients and greater than placebo-Study 108

Body Organ System	Adverse Events	Jornay PM (N=81)	Placebo (N=80)
Psychiatric disorders	Any insomnia	33%	9%
	Initial insomnia	14%	5%
	Middle insomnia	11%	4%
	Terminal insomnia	11%	1%
	Insomnia, NOS*	4%	1%
	Affect lability/ Mood swings	6%	1%
Metabolism and nutrition disorders	Decreased appetite	19%	4%
Nervous system disorders	Headache	10%	5%
	Psychomotor hyperactivity	5%	1%
Cardiovascular	Blood pressure diastolic increased	7%	4%
Gastrointestinal disorders	Vomiting	9%	0%
	Nausea	6%	0%
Skin and subcutaneous tissue disorders	Rash	2%	0%

*Insomnia, not otherwise specified

Conclusion

HLD200 is safe and effective, based on my review of the regulatory history, safety-related datasets from two efficacy trials, and Applicant's response to secondary endpoint questions during this review cycle.

Studies 107 and 108 had different study designs.

- The primary endpoints of efficacy for both studies were positive on statistical analysis and well-known, acceptable endpoints for assessing ADHD, namely the SKAMP and ADHD-RS-IV instruments.
- The (key) secondary endpoints of PREMB-R AM subscale (Study 107) and the BSFQ were acceptable for showing improved early morning functioning. This was proven by analyzing factor analysis of the line items questions on each scale, which were positive for HLD200.
- The safety data indicate that HLD200 was relatively well-tolerated. The stimulant-related adverse reactions, such as insomnia and decrease appetite, between Study 107 and 108 were substantially different in the respective,

double-blind treatment phases due to Study 107 having a 6-week, open-label, lead-in phase allowing patients to tolerate HLD200 and optimize their dose.

The safety review focused on insomnia because of the novel formulation of methylphenidate having delayed-release for 6 to 8 hours, then extended-release throughout the day time. Both studies indicate a greater amount of initial insomnia (6% in Study 107 and 14%in Study 108) compared to middle or terminal insomnia. Based upon adult pharmacokinetic data, it is unlikely that HLD200 is leaking early, upon taking the drug in the evening. The initial insomnia may be related to the overall duration of the formulation in pediatrics keeping the patients from falling asleep the next evening.

The ICH EI guideline recommends a safety database size of at least 100 patients for 1 year for drugs used in chronic conditions. However, the size of the safety database (119 + 117= 236 patients) is adequate because methylphenidate is long-known drug and no unexpected adverse events were reported. The Applicant did not conduct a long-term safety study in support of this 505(b)(2) NDA application. This is acceptable because the safety signals of insomnia and decreased appetite decreased over time and there was not a signal for decreased weight in children 6 to 12 years that needed monitoring over time.

Post Marketing Requirement Recommendation

During the original NDA review cycle, the review team met with the Pediatric Review Committee (PeRC) to discuss Pediatric Research Equity Act (PREA) post marketing requirements (PMRs). The following trials were recommended on July 19, 2017:

- PeRC concurred with the partial waiver in ages 0 to 3 years because studies are impossible or highly impractical and to the deferral in ages 4 to 5 years. Safety and efficacy from 6 to 12 years can be generalized to adolescent patients without the need for any additional clinical data;
- In the deferred efficacy and safety study in 4 to 5 years, the pharmacokinetic study would need to be designed such that it captures the peaks (not necessarily intensive PK); and
- A long-term safety study should be required in all study patients, 4 years and older.

During this Class 1 resubmission review of HLD200, the review team decided to require the following PREA PMR:

A Phase 3, 3-Week, Double-blind, Randomized, Placebo-controlled, Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Evening-dosed Jornay PM (methylphenidate hydrochloride) extended-release in Children Aged 4 to 5 With Attention Deficit Hyperactivity Disorder (ADHD).

We will advise the Applicant to plan to obtain adequate sparse PK sampling in the planned safety and efficacy study in children 4-5 years. Ensure that we get information about drug levels at early mornings (to capture any early drug release), at around T_{max} and at evenings prior to sleep (to obtain residual drug levels at sleep times). We will review the PK sampling in the PMR protocol after approval of the drug and labeling.

Package Insert Labeling Recommendations

Please refer to the approved label. The Adverse Events (6.0) and Clinical Trials (14) sections of the label were edited from the Applicant's proposed label dated June 8, 2018, which was in response to our July 27, 2017, Complete Response action. In Section 6, the differences in adverse event rates between the two pivotal trials was explained. In Section 14, because we were persuaded by the secondary endpoints for improved early morning functioning, the secondary endpoints are described. The HLD200 package insert is the first ADHD medication to list those instruments.

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/

NANCY C DICKINSON
08/07/2018

BERNARD A FISCHER
08/08/2018
Acting Lead Medical Officer