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Stimulant Medication With Evening Dosing to Address Early-Morning Functioning Impairments in ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder with increasing prevalence of diagnosis in children and adolescents.^{1,2} It is marked by behavioral symptoms that interfere with functioning or development, such as inattention, restlessness, disruptiveness, impulsivity, noncompliance to instruction, and disorganization.³ The early-morning routine is especially challenging for patients with ADHD as symptoms can impair the ability to perform activities during the period between waking up and the time they leave for school.^{4,5} In 2 independent, internet-based surveys, more than 75% of caregivers of children with ADHD rated the severity of their child's early-morning functioning impairment as moderate-to-severe.^{4,5}

Stimulant medications are available to help control ADHD symptoms, and are offered in a variety of formulations.⁴ Immediate-release (IR) formulations are designed to last approximately 3 to 4 hours after dosing, and often require 2 to 3 daily doses to provide coverage throughout the day.^{4,6,7} Longer-acting, extended-release (ER) medications are typically dosed once daily in the early morning to control symptoms during the in-school and after-school hours.^{4,6} The initial onset of action for ER medications may require up to 2 hours, and therefore, caregivers may try to adjust medication dosing schedules in an effort to achieve early-morning symptom coverage.^{4,6}

In the surveys described earlier, approximately half of caregivers of children with ADHD reported adopting workarounds such as waking children early to administer ADHD medications.^{4,5} However, the practice of waking children early to dose medication may be disruptive to the child's sleep and shorten the duration of medication coverage, potentially to the detriment of symptom control at the end of the day.

Innovative treatment options that provide therapeutic drug levels during the early morning are important to help address functional impairments among children and adolescents with ADHD during these critical hours. Pharmacists have a key role in working with patients, caregivers, and health care providers to increase awareness of current treatment options, such as JORNAY PM™ (methylphenidate hydrochloride [HCl] extended-release capsules), to control ADHD symptoms that occur during the early-morning hours.

JORNAY PM™

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of ADHD in patients 6 years and older.⁸ It is the first and only stimulant medication for ADHD that is dosed in the evening.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

DELEXIS® Drug Delivery Platform

JORNAY PM is designed using Delayed-Release and Extended-Release Drug Delivery Technology (DELEXIS), which allows for its unique evening dosing. The DELEXIS drug delivery system incorporates advanced microbead technology composed of 2 functional film coatings surrounding a methylphenidate core.^{9,10}

IMPORTANT SAFETY INFORMATION

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CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products.

- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

- Serious Cardiovascular Reactions:** Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, coronary artery disease, and other serious cardiac problems.

INFORMATION for the PHARMACIST

TABLE. JORNAY PM CLINICAL EFFICACY IMPROVEMENT OF ADHD SYMPTOMS IN THE EARLY MORNING AND THROUGHOUT THE DAY, AND INTO THE EVENING^{8,11,12}

	Awakening and Before School (early morning)		At School (daytime)	Throughout the Day (daytime to evening)	After School to Bedtime (late afternoon to evening)
ADHD assessment tool	PREMB-R AM	BSFQ	SKAMP	ADHD-RS-IV	PREMB-R PM (This end point was not adjusted for multiplicity).
Purpose of assessment tool	Assesses difficulties at home with before-school activities and behaviors during the early morning	Measures difficulty with early-morning activities or behaviors from awakening to leaving home for school (6 AM to 9 AM)	Measures impairment of behaviors in a classroom setting during the school day	Measures severity of ADHD symptoms throughout the day	Assesses difficulties at home or other activities after school in the late afternoon, evening, and bedtime
Assessment tool items and scoring	Morning subscale: 3 items rated on a scale of 0 (none) to 3 (a lot)	20 items rated on a scale of 0 (none) to 3 (severe)	13 items rated on a scale of 0 (normal/no impairment) to 6 (maximal impairment)	18 items (corresponds to the 18 <i>DSM-IV</i> ADHD symptoms) rated on a scale of 0 (none) to 3 (severe)	Evening subscale: 8 items rated on a scale of 0 (none) to 3 (a lot)

Results

Study 1^a

Mean baseline score (SD)

Placebo (n = 53)	5.7 (2.26)	N/A	16.6 (4.00)
JORNAY PM (n = 64)	5.8 (2.60)	N/A	17.6 (4.30)

LS mean (SE) at end of treatment

Placebo (n = 53)	2.7 (0.27)	20.7 (1.22)	9.3 (0.81)
JORNAY PM (n = 64)	0.9 (0.27)	14.8 (1.17)	6.1 (0.78)
P-value ^b	<0.001	<0.001	0.003

Study 2^c

Mean baseline score (SD)

Placebo (n = 80)	5.8 (2.20)	n = 78	44.9 (10.20)	43.5 (6.84)	16.6 (4.40)	n = 78
JORNAY PM (n = 81)	6.4 (2.24)	n = 81	44.2 (10.28)	43.1 (7.33)	17.4 (4.16)	n = 81

LS mean (SE) at end of treatment

Placebo (n = 80)	3.6 (0.27)	n = 75	28.4 (1.73)	n = 67	31.2 (1.60)	n = 67	12.2 (0.66)	n = 75
JORNAY PM (n = 81)	2.1 (0.26)	n = 79	18.7 (1.63)	n = 78	24.1 (1.50)	n = 78	9.4 (0.64)	n = 79
P-value ^b	<0.001		<0.001		0.002		0.002	

ADHD indicates attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale-IV; BSFQ, Before School Functioning Questionnaire; *DSM-IV*, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ITT, intention-to-treat; LS, least squares; N/A, not available; PREMB-R AM, Parent Rating of Evening and Morning Behavior-Revised morning subscale; PREMB-R PM, Parent Rating of Evening and Morning Behavior-Revised evening subscale; SD, standard deviation; SE, standard error; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham.

^aStudy 1 was conducted in children aged 6 to 12 years with ADHD. After a 6-week open-label treatment optimization phase, patients entered a 1-week, double-blind, controlled test phase during which patients were randomized to continue taking their optimized dose of JORNAY PM (20 mg, 40 mg, 60 mg, 80 mg, or 100 mg) or switch to placebo. Efficacy endpoints were assessed following 1 week of double-blind treatment.

^bP-value indicates the treatment difference between JORNAY PM and placebo groups in LS mean total scores at endpoint.

^cStudy 2 was conducted in children aged 6 to 12 years with ADHD. In this 3-week, double-blind, placebo-controlled study, patients were randomized to an evening dose of JORNAY PM or placebo. JORNAY PM was initiated at 40 mg for one week with scheduled titration as medically indicated and tolerated to 60 mg and 80 mg at Week 2 and 3, respectively. Efficacy endpoints were assessed following 3 weeks of treatment.

Please see additional Important Safety Information for JORNAY PM, including Boxed Warning, throughout this article.

INFORMATION for the PHARMACIST

Each capsule of JORNAY PM contains hundreds of microbeads, and each microbead has the following composition^{9,10}:

- **Delayed-release layer**, the outermost layer, limits the overnight release of methylphenidate.
- **Extended-release layer** controls the release from early morning and helps the drug last throughout the day.
- **Drug-loaded core** is coated with methylphenidate HCl.

When JORNAY PM is taken as a single dose in the evening, the DELEXIS drug delivery technology delays methylphenidate release until early the next morning, approximately 8 to 10 hours after dosing.⁸⁻¹⁰ In clinical trials of JORNAY PM, less than 5% of the methylphenidate dose was released within the first 10 hours after evening administration.^{9,10} After the delayed-release phase, absorption of methylphenidate rapidly increased, peaked approximately 14 hours after dosing, and gradually declined throughout the rest of the day.^{9,10}

Clinical Efficacy

The clinical efficacy and safety of JORNAY PM was evaluated in two phase 3, multicenter, randomized, double-blind, placebo-controlled studies of pediatric patients aged 6 to 12 years with a diagnosis of ADHD based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.^{8,11,12} ADHD symptoms were evaluated using 5 validated assessment tools, of which 3 were novel rating scales evaluating ADHD symptoms during the early-morning routine and evening and were validated specifically for the JORNAY PM clinical trials.^{13,14} As shown in the TABLE, treatment with JORNAY PM resulted in significant reduction of ADHD symptoms compared with placebo. Improvements in ADHD symptoms were observed between the hours of 6 AM to 9 AM, and these improvements lasted throughout the rest of the day.^{8,11,12}

Safety

JORNAY PM has a safety profile generally consistent with those of other methylphenidate products and was well tolerated in both clinical studies. The most common adverse reactions (ARs), reported in 5% or more of pediatric patients aged 6 to 12 years treated with

JORNAY PM and at about twice the rate of placebo, included appetite suppression, insomnia, headache, psychomotor hyperactivity, and mood swings.^{8,11,12} Based on accumulated data from other methylphenidate products, the most common ARs reported in 5% or more of pediatric and adults patients and at about twice the rate of placebo, are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.⁸

ROLE OF THE PHARMACIST

Pharmacists have an important role in counseling patients and their caregivers regarding the dosing and administration of JORNAY PM.

Starting Dose

JORNAY PM should be taken orally once daily at the same time each evening and should not be taken in the morning. JORNAY PM is available in 5 dose strengths (20-mg, 40-mg, 60-mg, 80-mg, and 100-mg capsules) with different physical distinguishing features. The recommended starting dose of JORNAY PM for patients 6 years and older is 20 mg once daily at 8 PM. The timing of administration can be adjusted between 6:30 PM and 9:30 PM to optimize tolerability and efficacy the next morning and throughout the day. The dosage may be titrated weekly in increments of 20 mg to the desired therapeutic effect, up to a maximum dose of 100 mg daily. Daily doses above 100 mg have not been studied and are not recommended. Following determination of the optimal administration time, advise patients to take their dose at approximately the same time each evening.⁸

The bioavailability of JORNAY PM is approximately 74% of that of the same daily dose of IR methylphenidate products; therefore, it cannot be substituted for other methylphenidate products on a milligram-per-milligram basis. Patients should be advised that JORNAY PM is not interchangeable with other ADHD medications. Patients switching from another methylphenidate product should be counseled to discontinue treatment with the other product before starting JORNAY PM. The appropriate dose of JORNAY PM should be determined via titration as previously described.⁸

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Blood Pressure and Heart Rate Increases:** CNS stimulants may cause an increase in blood pressure and heart rate. Monitor all patients for hypertension and tachycardia.
- **Psychiatric Adverse Reactions:** CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychiatric disorder and may induce a manic or mixed episode in patients with bipolar disorder. In patients with no prior history of psychotic illness or mania, CNS stimulants, at recommended doses, may cause psychotic or manic symptoms.
- **Priapism:** Prolonged and painful erections, sometimes requiring intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism has also appeared during a period of drug withdrawal. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.
- **Peripheral Vasculopathy, including Raynaud's Phenomenon:** CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
- **Long-Term Suppression of Growth:** CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor height and weight at appropriate intervals in pediatric patients.

INFORMATION for the PHARMACIST

Missed Doses

Advise patients that if they forget to take their dose of JORNAY PM at the regularly scheduled time, they should take it as soon as they remember that same evening. A missed dose should not be taken in the morning. If a patient remembers the missed dose the following morning, the missed dose should be skipped, and the next dose should be taken that evening at the usual time.⁸

Administration Options

JORNAY PM may be taken without regard to meals; however,

patients should be advised to take each dose the same way—either always with food or always without food. JORNAY PM capsules may be swallowed whole, or the capsules may be opened and sprinkled onto applesauce. As the dose of a single capsule should not be divided, advise caregivers who are using the sprinkled administration method that the contents of the entire capsule should be sprinkled onto the applesauce and taken immediately. The mixture cannot be stored, and the patient must swallow the mixture right away without chewing.⁸

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

- Based on accumulated data from other methylphenidate products, the most common ($\geq 5\%$ and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.
- Additional adverse reactions ($\geq 5\%$ and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings.

PREGNANCY AND LACTATION

- CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion.
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition. Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Please see additional safety information in the Brief Summary of Prescribing Information for JORNAY PM on adjacent pages.

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