



## Delayed-Release and Extended-Release Methylphenidate Capsules for Morning Control of Attention-Deficit/Hyperactivity Disorder Symptoms

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More than a dozen methylphenidate preparations are currently available in the United States for the treatment of attention-deficit/hyperactivity disorder (ADHD), each offering a difference in the pattern of drug release and duration of symptom control that may prove advantageous for an individual patient and family. The most recent addition, delayed-release and extended-release methylphenidate (DR/ER MPH) capsules (Jornay PM™) was approved by the Food and Drug Administration (FDA) on August 10, 2018 as the first product designed for administration at bedtime.<sup>1</sup> This new product was developed to avoid the up to 2 hour delay in early morning ADHD symptom control that may occur with other extended-release MPH products. It is currently approved for patients ages 6 years and older, and is designed to be given at approximately 8:00 pm to provide effective symptom control upon awakening.<sup>1-4</sup>

### Mechanism of Action

Central nervous system (CNS) stimulants have been used in the management of ADHD for over 50 years. Methylphenidate is believed to produce improvement in ADHD symptoms by blocking the reuptake of norepinephrine and dopamine in presynaptic neurons, increasing concentration of these neurotransmitters in the extraneuronal space. During the past two decades, advances in pharmaceuticals research has resulted in the creation of delayed and extended-release dosages forms that have lengthened the duration of symptom control provided by a single dose from 4 to 12-13 hours. In addition, new products have expanded the available methods for administration, ranging from capsules that can be opened to allow extended-release beads to be sprinkled on food for children unable to swallow a capsule or tablet to transdermal patches and extended-release oral liquids.<sup>2</sup>

The DR/ER MPH capsule is the first drug to reach the market that uses Ironshore Pharmaceutical's Delexis® drug delivery platform.<sup>1-3</sup> The capsules contain microbeads with a methylphenidate-coated core surrounded by two different functional film coatings that work synergistically to control drug release. The outer layer contains hydrophobic, hygroscopic, and pH-dependent polymers that delay the initial release of drug until it reaches the colon, approximately 8 to 10 hours after administration, allowing normal sleep. The inner layer of hydrophobic soluble polymers regulates the permeability of the water into the drug core, controlling the rate of dissolution and prolonging the absorption of MPH in the colon, providing an extended release of drug throughout the school day and into the evening similar to other once-daily MPH products.

### Pharmacokinetics

The pharmacokinetic profile of DR/ER MPH was further defined by Childress and colleagues using data from two premarketing trials: a single-dose phase 1 study conducted in 12 healthy adult volunteers and a single-center open-label phase 1/2 study which included 29 patients with ADHD, 18 adolescents between 13 and 17 years of age and 11 children between 6 and 12 years of age.<sup>3</sup> The patients in both studies received a dose of 54 mg, providing a higher range of weight-based doses in younger patients: 0.54-0.85 mg/kg in the adults, 0.52-1.04 mg/kg in the adolescents, and 1-2.08 mg/kg in the children. The primary pharmacokinetic parameters evaluated the rate and extent of methylphenidate absorption, assessed through the maximum serum concentration ( $C_{max}$ ), time to maximum serum concentration ( $T_{max}$ ) and the area under the concentration-time curve (AUC). The parameters were calculated using noncompartmental analysis.

As anticipated based on earlier investigations, administration of the DR/ER MPH dose was followed by an 8 to 10-hour period in which there was no significant release of methylphenidate into the systemic circulation. The authors noted no premature release of the drug and no adverse effects on the sleep cycle. After that period, methylphenidate serum concentrations reflected an extended controlled release of drug from the coated beads contained in the capsule. Pharmacokinetic values without weight-adjusting the dose were higher in children, with a mean and coefficient of variation (%)  $C_{max}$  of 11.6 ng/mL (36.3) compared to 7.2 ng/mL (23.7) in adolescents and 6.0 ng/mL (24) in adults. Mean AUC also differed among the age groups, with a mean of 205.5 ng•hr/mL (39.1) in the children, compared to 105.5 ng•hr/mL (30.0) and 83.4 ng•hr/mL (27.1) in the adolescents and adults, respectively. Time to maximum concentrations was similar among all three groups: 17.7 hours (14.1), 17.1 hours (14.5), and 15.6 hours (11.1).

When the results were normalized for dose and body weight, the pharmacokinetic values were similar in all three groups. Mean  $C_{max}$  values were 7.4 ng/mL/mg/kg (30.1) in the children, 8.8 ng/mL/mg/kg (34.5) in the adolescents, and 9.1 ng/mL/mg/kg (35.2) in the adults. Mean values for  $T_{max}$  were also similar; 17.7 hours (14.1), 17.1 hours (14.5), and 15.6 hours (11.1) in the three age groups, respectively. Mean AUC values were 129.7 ng•hr/mL/mg/kg (27.3), 129.4 ng•hr/mL/mg/kg (34.8), and 126.5 ng•hr/mL/mg/kg (35.5). Based on these findings, the authors concluded that use of non-weight-based dosing was appropriate for dose initiation.

Administration with food has been shown to have little effect on DR/ER MPH absorption in adults, with a high-fat meal given with the evening dose producing only a 14% reduction in maximum serum concentration compared to that of a dose taken in a fasted state.<sup>2</sup> Median time to maximum concentration was delayed by approximately 2.5 hours in the fed patients. Neither change was considered clinically significant. The absorption characteristics of DR/ER MPH were also no different whether study subjects took the whole capsule or when the capsule contents were sprinkled on applesauce.

Methylphenidate is metabolized by de-esterification to alpha-phenyl-piperidone acetic acid. The elimination half-life of methylphenidate in adults is approximately 5-6 hours.<sup>2</sup> There is minimal effect of renal insufficiency on methylphenidate clearance. The impact of hepatic impairment on DR/ER MPH is not yet known.

### Clinical Experience

A total of 278 children between 6 and 12 years of age with a confirmed diagnosis of ADHD were enrolled in two phase 3 randomized, double-blind, placebo-controlled trials.<sup>2,5</sup> The first was a 6-week open-label dose-optimization study with 117 patients receiving doses of 50 to 100 mg (mean dose 50 mg), followed by a 1-week double-blind, placebo-controlled withdrawal phase in which patients were randomized to continue their optimized DR/ER MPH dose or changed to placebo. The mean dose during this study in the treated patients was 67 mg. At the end of the final week, patients were evaluated in a simulated classroom setting over a 12-hour period using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP). Scores range from 0 (no impairment) to 78 (maximal impairment). The primary endpoint was a model-adjusted average of all SKAMP scores over the 12-hour period. The secondary endpoint was the morning component of the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM) to evaluate early morning symptom control. Scores range from 0 (no ADHD symptoms) to 9 (severe symptoms).

The primary endpoint, the adjusted average of the SKAMP scores, was significantly lower in the DR/ER MPH group compared to the controls ( $14.8 \pm 1.17$  compared to  $20.7 \pm 1.22$ , difference  $-5.9$ , 95% CI  $-9.1, -2.7$ ). The differences in SKAMP scores between the groups were significant at 9 am, 10 am, noon, 2 pm, 4 pm, 6 pm, and 7 pm. The secondary endpoint, mean PREMB-R AM score, was also statistically significantly different between the groups.

The second study was a 3-week multicenter, randomized, double-blind, parallel-group study which enrolled 161 patients 6-12 years of age.<sup>5</sup> This study was published by Pliszka and colleagues, writing for the HLD200-108 Study Group, in the August 2017 issue of the *Journal of Child and Adolescent Psychopharmacology*. Patients were randomized to a dose of 40 mg, 60 mg, or 80 mg given once daily in the evening. The primary endpoint for this study was the change from baseline in the ADHD Rating Scale-IV Total Score (ADHD-RS-IV). Possible scores for this scale range from 0 (no ADHD symptoms) to 54 (severe symptoms of both hyperactivity and inattentiveness).

The mean baseline ADHD-RS-IV for the participated was  $43.4 \pm 7.1$ . Secondary endpoints included the change from baseline in the Before-School Functioning Questionnaire (BSFQ) and the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R PM and AM) scores. The BSFQ is a 20-question assessment performed by the clinician with the patient's

parent or caregiver. The questionnaire was developed to assess early morning behaviors that may affect preparation for school. Scores on the BSFQ range from 0 (no difficulty) to 60 (severe difficulty). The 3-item PREMB-R AM score ranges from 0 (no difficulty) to 9 (maximum difficulty), with the 8-item PM score ranges from 0 to 24.

At the end of the 3-week study, the primary endpoint, ADHD-RS-IV scores, showed significantly greater improvement in the treatment group compared to the placebo group, with a least squares mean (SE) score of 24.1 (1.50) versus 31.2 (1.60),  $p = 0.002$ . The differences between the groups were also significant at the end of weeks 1 and 2 ( $p < 0.001$  and  $p = 0.002$ ). Results of the BSFQ also showed statistically significant improvement in symptoms for all three weeks of the study, with a least squares mean of 18.7 (1.63) in the DR/ER MPH group versus 28.4 (1.73) in the controls ( $p < 0.001$ ) at the final evaluation. For comparison, the mean BSFQ scores at baseline for the treatment and control groups were  $44.2 \pm 10.28$  and  $44.9 \pm 10.20$ , respectively. Similar improvement was shown in the PREMB-R AM scores, 2.1 (0.26) versus 3.6 (0.27) and the PREMB-R PM scores, 9.4 (0.64) versus 12.2 (0.66), ( $p < 0.001$  and  $p = 0.002$ , respectively).<sup>5</sup>

#### Warnings and Precautions

Methylphenidate administration has been associated with hypersensitivity reactions, including angioedema and anaphylaxis, in a small number of patients.<sup>2</sup> As with all CNS stimulants, DR/ER MPH carries a black box warning for its high potential for abuse and dependence. Patients should be evaluated for signs of abuse or dependence throughout therapy, as well as assessed for the risk for overuse and potential overdose. Patients with physical dependence after long-term high-dose therapy may exhibit symptoms of withdrawal after sudden discontinuation of therapy, with changes in sleep patterns, dysphoria or depression, or agitation.

Methylphenidate may exacerbate psychiatric symptoms or induce a manic episode in patients with bipolar disorder. While the incidence of these reactions is small (approximately 0.1% of patients), it is recommended that all patients be screened for a history of behavioral disorders.<sup>2</sup>

In adults, stimulant medications have been associated with myocardial infarction, stroke, peripheral vasculopathy, and sudden cardiac death.<sup>2</sup> Cases have also been reported in children with underlying structural cardiac defects. When starting any stimulant therapy, a thorough patient and family history should be performed for the presence of heart defects, arrhythmias, or cases of

sudden death. Stimulants should not be used in patients with serious cardiac disease, including structural cardiac abnormalities, cardiomyopathy, or serious arrhythmias. Blood pressure and heart rate should be obtained at baseline and with any subsequent dose adjustments. While most patients have a clinically insignificant increase (2-4 mmHg and 3-6 bpm, respectively), some patients have experienced larger increases.

#### Adverse Effects

The most commonly reported adverse reactions with all methylphenidate products include decreased appetite, insomnia, nausea, vomiting, abdominal discomfort or pain, weight loss, anxiety, dizziness, irritability, labile affect, tachycardia, and increased blood pressure.<sup>2</sup>

Additional adverse reaction data for DR/ER MPH is available from a summary of the 280 children (6-12 years of age) enrolled in the two premarketing clinical trials.<sup>2,3,5</sup> In the first study, a 6-week open-label dose-optimization phase was followed by a 1-week placebo-controlled withdrawal. The adverse reactions reported in more than 5% of patients during the open-label component included insomnia (41%), decreased appetite (27%), affect lability/mood swings (22%), headache (19%), upper respiratory tract infection (17%), abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment for behavioral changes, panic attacks, agitation, or aggression. There were no differences in any of the adverse effects between the treatment group and the controls during the comparison component of the study.

The Pliszka study described earlier provides additional safety information obtained from 161 patients 6-12 years of age.<sup>5</sup> Adverse reactions were reported in 56 (69.1%) of the children in the DR/ER MPH group and 39 (48.8%) of those in the placebo group. There were no serious adverse reactions attributed to the drug. Five patients discontinued participation in the study, including one patient in the DR/ER MPH group (1.2%) who developed mood swings and four patients in the placebo group: two who developed irritability, one with gastrointestinal discomfort and enuresis, and one with dizziness, difficulty sleeping, somnolence, and tremor. The most common adverse reactions (occurring in > 5% of subjects) reported in the children receiving DR/ER MPH were insomnia (35.8%), decreased appetite (18.5%), headache (9.9%), vomiting (8.6%), increased diastolic blood pressure (7.4%), and nausea (6.2%).

Mild sleep disturbances were reported in 82.8% of the DR/ER MPH patients and 72.7% of the

placebo patients, but most were transient and self-resolved during the study. Four of the patients in the DR/ER MPH had their dose reduced with resolution of symptoms. The mean change from baseline in diastolic blood pressure was  $2.5 \pm 9.06$  mmHg, in systolic blood pressure was  $1.5 \pm 12.18$  mmHg, and heart rate was  $3.5 \pm 11.49$  bpm. None of the changes in blood pressure or heart rate were considered clinically significant.<sup>5</sup>

Stimulants have been associated with slowing of growth velocity.<sup>2</sup> In a 14-month placebo-controlled comparison study, methylphenidate produced a temporary slowing in growth, with an average difference of 2 cm less growth in height and 2.7 kg less weight gain over 3 years. These effects do not continue if the drug is discontinued, but catch-up growth does not appear to occur. As in patients receiving other methylphenidate products, weight and height should be monitored during initiation to provide an accurate baseline, and during any medical visits during treatment. Families of patients exhibiting signs of appetite suppression should be aware of the need to provide additional opportunities for nutritious snacks to boost caloric intake. In patients with significant slowing of growth, stimulants should be discontinued.

#### Drug Interactions

All methylphenidate preparations are contraindicated in patients with a known hypersensitivity to any of the product components.<sup>2</sup> Methylphenidate is also contraindicated in patients who have taken a monoamine oxidase inhibitor (MAOI) within the past 14 days because of the risk for hypertensive crisis as the result of an inability to metabolize methylphenidate.

#### Availability and Dosing Recommendations

The Jornay PM™ delayed-release and extended-release methylphenidate product has been approved, but is not yet available from the manufacturer. It is expected that the capsules will come in 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg strengths.<sup>2</sup> The recommended starting dose for DR/ER MPH in all patients is 20 mg taken once daily in the evening. The manufacturer suggests that treatment should be initiated with dose administration at 8:00 pm, but may be given between 6:30 and 9:30 pm to adjust to the patient's schedule. Once the optimal time has been established, the dose should be given at the same time every evening. The dose may be increased in 20 mg increments at weekly intervals until symptom control has been achieved. The recommended maximum is 100 mg; higher doses have not been studied to date. If the evening dose is missed, it should be given as soon as it is noticed up until the patient's bedtime. This product should not be given in the morning, as the

delayed effects would not provide adequate symptom control for the school day and would likely produce insomnia that night.

The DR/ER MPH capsule may be taken with or without food. For patients unable to swallow the capsule whole, it may be opened and the beads sprinkled onto applesauce. The MPH/applesauce mixture should be swallowed without biting down or chewing it. Capsule contents should not be divided, and once opened, the capsule contents should not be stored for later use. The capsules should be stored at room temperature and protected from humid environments. In patients transitioning from another methylphenidate product, the previous product should be discontinued and DR/ER MPH should be initiated the same day at a dose of 20 mg and titrated as described. Milligram-per-milligram substitution from another product to DR/ER MPH is not recommended.<sup>2</sup>

#### Summary

Bedtime administration of a stimulant medication may provide better early morning symptom control and improve morning routines for some families of children with ADHD. With the continued growth in the number of methylphenidate options currently available, pediatric healthcare providers have a variety of options to maximize treatment benefit for each patient with ADHD.

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