A novel, once-daily treatment option for patients with ADHD 6 years and older

JORNAY PM™

methylphenidate HCl CII

extended-release capsules

20mg 40mg 60mg 80mg 100mg

Now Available

The first and only ADHD stimulant dosed in the evening

Help your patients wake up ready for the day

When dosed in the evening, the delayed-release and extended-release technology of JORNAY PM enables the drug to be delivered in the early morning—and it lasts throughout the day

Mornings matter. Learn more at JORNAYpm.com and prescribe today.

Indication and Important Safety Information

INDICATION

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

IMPORTANT SAFETY INFORMATION

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.

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.
- *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.

ADVERSE REACTIONS

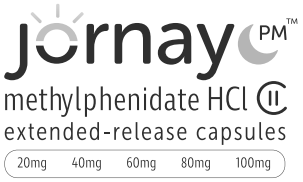
- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.
- Additional adverse reactions (≥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.

IRONSHORE PHARMACEUTICALS



JORNAY PM™ (methylphenidate hydrochloride) extended-release capsules, for oral use, CII Rx only

BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information

IMPORTANT SAFETY INFORMATION

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.

INDICATIONS AND USAGE

JORNAY PM is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

DOSAGE AND ADMINISTRATION

JORNAY PM should be taken only in the evening. Adjust the timing of administration between 6:30 pm and 9:30 pm to optimize the tolerability and efficacy the next morning and throughout the day.

The recommended starting dose for patients 6 years and above is 20 mg daily in the evening. Dosage may be increased weekly in increments of 20 mg per day up to a maximum daily dose of 100 mg.

Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce.

Do not substitute for other methylphenidate products on a milligram-per-milligram basis.

CONTRAINDICATIONS

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.

Concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of a monoamine oxidase inhibitor, because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for 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 for abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

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 cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, and other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with JORNAY PM.

Blood Pressure and Heart Rate Increases CNS stimulants may cause an increase in blood pressure (mean increase 2 to 4 mmHg) and heart rate (mean increase 3 to 6 bpm). Individuals may have larger increases. Monitor for hypertension and tachycardia.

Psychiatric Adverse Reactions Exacerbation of Pre-existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history. If such occur, consider discontinuing JORNAY PM. In a pooled analysis of studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared with 0 in placebo-treated patients.

Priapism Prolonged, painful erections, sometimes requiring surgery, have been reported with methylphenidate in both pediatric patients and adults. Priapism was not reported with drug initiation but developed after time on the drug, often after an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent, painful erections should seek immediate medical attention.

Peripheral Vasculopathy, including Raynaud's Phenomenon CNS stimulants, including JORNAY PM, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Long-term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth in pediatric patients. Careful follow-up of weight and height in patients ages 7 to 10 years who were randomized to either methylphenidate or placebo over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and placebo-treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth (on average, 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period. Closely monitor growth (weight and height) in children treated with CNS stimulants, including JORNAY PM. Patients not growing or gaining height or weight as expected may need their treatment interrupted.

ADVERSE REACTIONS

Clinical Trial Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. Clinical Trials Experience with JORNAY PM in Pediatric Patients (6 to 12 years) with ADHD The safety of JORNAY PM was evaluated in 280 patients (6 to 12 years of age) who participated in two controlled clinical studies of patients with ADHD. Study 1, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=125; mean dose 50 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue JORNAY PM (n=65) or switch to placebo (n=54). During the open-label JORNAY PM treatment phase, adverse reactions reported in > 5% of patients included: any insomnia (41%), decreased appetite (27%), affect lability (22%) headache (19%), upper respiratory tract infection (17%), upper abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment because of affect lability, panic attacks, and agitation and aggression. Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice. No difference occurred in the incidence of adverse reactions between JORNAY PM and placebo during the 1-week, double-blind, placebo-controlled phase. Study 2 was a 3-week, placebo-controlled study of JORNAY PM (n=81; mean dose 52mg) in pediatric patients 6 to 12 years. *Most Common Adverse Reactions* (incidence of ≥ 5% and at a rate at least twice placebo): any insomnia, decreased appetite, headache, vomiting, nausea, psychomotor hyperactivity, and affect lability or mood swings. One patient in the JORNAY PM group discontinued from the study due to mood swings. Table 1 provides the incidence of adverse reactions reported in Study 2 (incidence of 2% or more and at least twice placebo) among pediatric patients 6 to 12 years in a 3-week clinical trial.

Table 1: Adverse Reactions Occurring in ≥2% of JORNAY PM-treated Pediatric Patients and Greater than Placebo in a 3-Week ADHD Study (Study 2)

Body Organ System	Adverse Reaction	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, not specified	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%
Infections and infestations	Nasopharyngitis	3%	1%
	Pharyngitis streptococcal	3%	0%
Injury, poisioning and procedural complications	Contusion	3%	0%
Musculoskeletal and procedural complications	Back pain	3%	0%
Skin and subcutaneous tissue disorders	Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during postapproval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole
Eye Disorders: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Hyperpyrexia
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, Eruptions, and Exanthemas
Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, Severe hepatic injury
Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis
Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs
Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania
Urogenital System: Priapism
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema
Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer JORNAY PM concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary Published studies and postmarketing reports on methylphenidate use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 2 and 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis, respectively. However, spina bifida was observed in rabbits at a dose 31 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 3.5 times the MRHD given to adolescents. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies. Clinical Considerations *Fetal/Neonatal Adverse Reactions* CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Data *Human Data* A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. *Animal Data* In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 31 times the MRHD of 100 mg/day given to adolescents on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (9 times the MRHD given to adolescents on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m^2 basis, which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis).

Lactation Risk Summary Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. 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. Clinical Considerations Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Pediatric Use The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established. The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Long-Term Suppression of Growth Growth should be monitored during treatment with stimulants, including JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted. Juvenile Animal Toxicity Data Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with $\geq$ 50 mg/kg/day (approximately $\geq$ 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Geriatric Use JORNAY PM has not been studied in patients older than 65 years of age.

DRUG ABUSE AND DEPENDENCE

Controlled Substance JORNAY PM contains methylphenidate, a Schedule II controlled substance.

Abuse CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death. To reduce the abuse of CNS stimulants including JORNAY PM, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for JORNAY PM use.

Dependence Tolerance Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including JORNAY PM. Dependence Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants, including JORNAY PM. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include: dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

OVERDOSAGE

Signs and Symptoms Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

Management of Overdose Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosages. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

IRONSHORE PHARMACEUTICALS

The American Journal of Psychiatry Residents' Journal

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Beginning in 2019, the *Residents' Journal* (RJ) will convert to a quarterly publication schedule (September, December, March, and June). In this manner, volume years will correspond with academic years and the tenure of each RJ editorial board. Volume 15, Issue 1 will appear online in September 2019

In the meantime, continue to follow RJ on social media for updates on what's to come, and look for our podcasts!

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