PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

JORNAY PM®

methylphenidate hydrochloride delayed-release and extended-release capsules

Delayed-release and extended-release Capsules, 20 mg, 40 mg, 60 mg, 80 mg and 100 mg methylphenidate hydrochloride, Oral

Manufacturer's Standard /

Central Nervous System Stimulant

Ironshore Pharmaceuticals & Development, Inc.
10 Market Steet, Suite 715
Camana Bay, Grand Cayman
Cayman Islands

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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JORNAY PM® (methylphenidate hydrocholoride delayed-release and extended-release capsules) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- Children (6-12 years of age)

Long Term Use

The effectiveness of JORNAY PM for long-term use (i.e., for more than 3 weeks), has not been systematically evaluated in placebo-controlled trials. Therefore, the health care professional who elects to prescribe JORNAY PM for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see 4 DOSAGE AND ADMINISTRATION).

Need for Comprehensive Treatment Program

JORNAY PM is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the health care professional's assessment of the chronicity and severity of the patient's symptoms.

1.1 Pediatrics

Pediatrics (<6 years of age): JORNAY PM should not be used in children under 6 years of age. The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use in patients under 6 years of age.

Pediatrics (6 – 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JORNAY PM in pediatric patients aged 6-12 years have been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment).

Pediatrics (13 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JORNAY PM in pediatric patients aged 13-17 years have not been established; therefore, Health Canada has not authorized an indication for use in ages 13-17 years.

1.2 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

JORNAY PM is contraindicated in:

- Patients who are hypersensitive to methylphenidate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Additionally, JORNAY PM is contraindicated in patients with the following:

- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Anxiety, tension.
- Agitation.
- Thyrotoxicosis.
- Advanced arteriosclerosis.
- Symptomatic cardiovascular disease.
- Moderate to severe hypertension.
- Glaucoma.
- History of drug abuse.
- Pheochromocytoma.
- Patients with motor tics and/or family history or diagnosis of Tourette's syndrome. See 7 WARNINGS AND PRECAUTIONS, Neurologic.
- Receiving 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. See 9 DRUG INTERACTIONS.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Drug Dependence – Like other stimulants, JORNAY PM has the potential to be abused, leading to dependence and tolerance (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- JORNAY PM should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted to the lowest effective dosage since individual patient response to JORNAY PM varies widely.
- Advise patients to take JORNAY PM consistently, either with or without food.
- JORNAY PM should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Theoretically, there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.
- Patients who are considered to need extended treatment with JORNAY PM should undergo periodic evaluation of their cardiovascular status (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

4.2 Recommended Dose and Dosage Adjustment

- JORNAY PM is given orally once daily in the evening. JORNAY PM should not be taken in the morning.

- **Patients New to Methylphenidate**

  The recommended starting dose of JORNAY PM for patients aged 6-12 years is 20 mg once daily in the evening. JORNAY PM should not be taken in the morning. The dose may be adjusted up or down weekly by 20 mg. Daily doses above 100 mg and/or 3.7 mg/kg (based on most recently assessed weight) have not been studied and are not recommended.

  Initiate dosing at 8:00 p.m. Adjust the timing of administration between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and efficacy the next morning and throughout the day. In clinical trials of patients aged 6 to 12 years, the most common dosing time (>70% of patients) was 8:00 p.m., with an allowed range between 6:30 p.m. and 9:30 p.m. Following determination of the optimal administration time, advise patients to maintain a consistent dosing time.

- **Patients Currently Taking Methylphenidate**

  If switching from other methylphenidate products, discontinue that treatment, and titrate with JORNAY PM using the titration schedule described above.

  Do not substitute JORNAY PM for other methylphenidate products on a milligram-per-milligram basis because these products have different pharmacokinetic profiles from JORNAY PM and may have different methylphenidate base composition.

- **Long-term Use**

  There is no evidence available from controlled trials to indicate how long a patient with

ADHD should be treated. Pharmacological treatment of ADHD may be needed for extended periods. The safety and efficacy of JORNAY PM were studied in two placebo-controlled randomized trials in children with ADHD. One study had a 6 week open-label dose optimization phase followed by a one week placebo-controlled randomized withdrawal period. The other study was a 3 week, randomized, placebo-controlled parallel group study (see 14 CLINICAL TRIALS).

The clinician who elects to use JORNAY PM for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or, if necessary, discontinue the drug. If little or no improvement is observed after appropriate dosage adjustment over a one-month period, discontinue drug.

4.4 Administration

JORNAY PM may be taken whole, or the capsule may be opened, and the entire contents sprinkled onto applesauce. If the patient is using the sprinkled administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken consistently at the same time.

JORNAY PM should be consistently taken either with or without food. Taking JORNAY PM with a high-fat meal at night can delay methylphenidate absorption (see 10.3 Pharmacokinetics, Food Effect).

4.5 Missed Dose

Patients who miss their dose of JORNAY PM at the regularly scheduled time should take it as soon as they remember that same evening. If a patient remembers the missed dose the following morning, they should skip the missed dose and wait until their next scheduled evening administration. Patients should be instructed not to take a morning or afternoon dose and not to double the dose.

5 OVERDOSAGE

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

Management consists of providing supportive measures. The patient must be protected against self- injury and against external stimuli that would exacerbate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange. External cooling procedures may be required to reduce hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate overdosage has not been established. The prolonged release of methylphenidate from JORNAY PM capsules should be considered when treating patients with overdose.

Alcohol may induce the production of ethylphenidate. The amount of ethylphenidate production is proportional to the blood alcohol concentration (see 9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview). As with the management of all overdosage, the possibility of multiple drug ingestion, including alcohol, should be considered.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Delayed-release and Extended-Release Capsules / 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg / methylphenidate hydrochloride	dibutyl sebacate, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, mono- and di-glycerides, polysorbate 80, and talc.

JORNAY PM capsules also contain the following inactive ingredients for the capsule shell and imprint are listed in Table 2. All dosage strengths are supplied in bottles of 100 capsules.

Table 2: Capsule Shell and Imprint by Dosage Strength

Strength (mg)	Capsule Colour and Description	Non-medicinal Ingredients in Capsule Shell and Imprint
20 mg	Ivory opaque body and light green opaque cap (imprinted with “20 mg” in black on the body and “IRONSHORE” in black on the cap)	FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint.
40 mg	Ivory opaque body and blue-green opaque cap (imprinted with “40 mg” in black on the body and “IRONSHORE” in black on the cap)	FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint.
60 mg	White opaque body and powder blue opaque cap (imprinted with “60 mg” in black on the body and “IRONSHORE” in black on the cap)	FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint
80 mg	White opaque body and light blue opaque cap (imprinted with “80 mg” in black on the body and “IRONSHORE” in black on the cap)	FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint
100 mg	White opaque body and dark blue opaque cap (imprinted with “100 mg” in black on the body and “IRONSHORE” in white on the cap)	black iron oxide, FD&C Blue #1, hypromellose, red iron oxide, titanium dioxide, and black ink, and white ink for the imprint.

JORNAY PM delayed-release and extended-release capsules contain beads with two functional film coatings (outer delayed-release and inner extended-release) surrounding a methylphenidate hydrochloride drug layered core. Following an initial delay in release of methylphenidate of approximately 8-10 hours, methylphenidate is released at a controlled rate throughout the day

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

- Drug treatment is not indicated in all cases of ADHD and should be considered only in light of the complete history and evaluation. The decision to prescribe JORNAY PM should depend on the health professional's assessment of the chronicity and severity of the patient's symptoms. Treatment should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.
- All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities; b) use other stimulants; or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history (including assessment for a family history sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgement, further cardiovascular evaluation may be considered (e.g., electrocardiogram [ECG] and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.
- Fatigue: JORNAY PM should not be used for the prevention or treatment of normal fatigue states.
- Pharmacokinetic studies conducted with JORNAY PM show that there is approximately 17-36% residual methylphenidate in the blood at 24 hours.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY section.

Cardiovascular

- **Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems:**

  Children and Adolescents:

  Sudden death has been reported in association with stimulant drugs used for ADHD treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious cardiac problems. Although some serious heart problems

alone carry an increased risk of sudden death, JORNAY PM generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug (see 2 CONTRAINDICATIONS).

Adults:

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see 2 CONTRAINDICATIONS).

- **Pre-existing Cardiovascular and Cerebral Vascular Conditions:**

  Central Nervous System (CNS) stimulants should be used with caution in patients with a condition of the cardiovascular or cerebrovascular system, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with stimulants and monitored for new conditions of the heart or brain during the course of treatment.

- **Hypertension and other Cardiovascular Conditions:**

  Hypertension may occur during methylphenidate treatment in some patients. Caution is particularly indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction or hyperthyroidism.

  Blood pressure should be monitored at appropriate intervals in patients receiving stimulants, especially in patients with pre-existing conditions that may result in hypertension (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS).

  CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Some individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

- **Misuse and Cardiovascular events:**

  Misuse of stimulants of the CNS may be associated with sudden death and other serious cardiovascular adverse events.

- **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 with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Dependence/Tolerance

JORNAY PM should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronic abuse can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse.

Careful supervision is required during withdrawal from abuse since severe depression may occur. Withdrawal following chronic therapeutic use may require follow up.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that JORNAY PM does not adversely affect their ability to engage in such activities.

Endocrine and Metabolism

- **Long-Term Suppression of Growth:**

  CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

  Children in JORNAY PM ADHD Clinical Trials

  In a controlled study of JORNAY PM in children aged 6 to 12 years with ADHD, comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM, followed by a 1-week double-blind, placebo controlled phase whether patients continued on JORNAY PM or switched to placebo, the mean change in weight at the end of the 6 week dose optimization phase was -0.49 kg. The mean weight change from baseline to endpoint, the end of the double-blind phase, was -0.32 kg for patients receiving JORNAY PM compared to a weight gain of 0.18 kg for patients receiving placebo.

  In a 4-week controlled study of JORNAY PM in children aged 6 to 12 years with ADHD, mean weight change from baseline to endpoint was -0.28 kg for patients receiving JORNAY PM, compared to a 0.34 kg weight gain for patients receiving placebo.

Methylphenidate Use in Children with ADHD

Analysis of children growth criteria indicates that pediatric patients who received MPH once daily for 3 years had a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less gain in weight), without evidence of growth rebound during this development period compared to non-treated groups.

Closely monitor growth (height and weight) in JORNAY PM-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected should have their treatment interrupted.

Monitoring and Laboratory Tests

Periodic laboratory tests are advised during prolonged therapy. The tests should include, but not be limited to, haematological parameters, including complete blood count, differential and platelet counts, and liver enzymes.

Neurologic

- **Seizures:**

  There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of seizures and, very rarely, in patients with no prior EEG evidence or history of seizures. Clinical experience has shown that a small number of patients may experience an increase in seizure frequency when treated with methylphenidate. In the presence of seizures or suspected seizures, the drug should be discontinued.

- **Motor and Verbal Tics, and Worsening of Tourette's Syndrome:**

  CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported with other CNS stimulants. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate.

- **Serotonin toxicity / Serotonin syndrome:**

  Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with methylphenidate, including JORNAY PM, with concomitant use of serotonergic or dopaminergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Drugs).

  Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with JORNAY PM and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonergic Drugs). If serotonin toxicity is suspected, discontinuation of JORNAY PM and other serotonergic agents should be considered and appropriate treatment instituted.

Ophthalmologic

- **Acute Angle Closure Glaucoma**
  There have been reports of angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, JORNAY PM-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.
- **Increased intraocular pressure and glaucoma**
  There have been reports of elevation of intraocular pressure (IOP) and glaucoma associated with methylphenidate treatment. JORNAY PM is contraindicated in patients with glaucoma (see 2 CONTRAINDICATIONS).
- **Visual Disturbance:**

  Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported (see 8 ADVERSE REACTIONS).

Psychiatric

- **Pre-Existing Psychosis:**

  Administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder.
- **Screening Patients for Bipolar Disorder:**

  Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.
- **Emergence of New Psychotic or Manic Symptoms:**

  Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania, can be caused by stimulants at usual doses. If such symptoms occur,

consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

- **Aggression, Anxiety, and Agitation:**

  Patients with an element of agitation may react adversely; discontinue therapy if necessary.

  Aggressive behaviour, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behaviour or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour, marked anxiety, or agitation.

- **Suicidal Behaviour and Ideation:**

  There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour.

  Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/ optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen (see 8.5 Post-Market Adverse Reactions).

- **Depression:**

  JORNAY PM should not be used to treat severe exogenous or endogenous depression.

Reproductive Health: Female and Male Potential

- **Function**

  Priapism:

  Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products in both pediatric and adult patients (see 8.5 Post-Market Adverse Reactions).

  Priapism can develop after some time on methylphenidate, often subsequent to an increase in dose. Priapism has also appeared during a period of methylphenidate withdrawal (drug holidays or during discontinuation). Patients who develop abnormally

sustained erections or frequent and painful erections should seek immediate medical attention.

7.1 Special Populations

7.1.1 Pregnant Women

Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 62.5 times and 20 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Studies to establish safe use of methylphenidate in pregnant women have not been conducted. Therefore, JORNAY PM should not be given to pregnant women unless the potential benefit outweighs the risk to the fetus.

- **Embryo/Fetal/Neonatal Adverse Reactions**

  CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

7.1.2 Breast-feeding

A study conducted in rats indicated that the distribution profiles of methylphenidate in milk and plasma are similar. Case reports showed that methylphenidate was distributed into breast milk reaching a milk- to-plasma ratio of approximately 2.7 (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pregnancy and Breast-Feeding).

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded. A decision should be made whether to abstain from breast-feeding or to abstain from JORNAY PM therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

7.1.3 Pediatrics

Pediatrics (6 –12 years of age): Long-term effects of methylphenidate in children have not been well established (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

Pediatrics (<6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for children under six years of age.

Pediatrics (13 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JORNAY PM in pediatric patients aged 13-17 years have not been established; therefore, Health Canada has not authorized an indication for use in ages 13-17

years.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical trials with JORNAY PM, the most frequent adverse events (occurring at ≥10%) were insomnia, affect lability, headache, decreased appetite, increased diastolic blood pressure, and upper respiratory tract infection. There were no serious adverse events. Adverse events leading to discontinuation included affect lability, agitation, aggression, anxiety, panic attack, and mood swings.

8.2 Clinical Trial Adverse Reactions

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The clinical trial program for JORNAY PM methylphenidate hydrochloride delayed-release and extended-release capsules) included exposures in 242 patients (6-12 years of age) in two clinical studies in patients with ADHD. Study 1 comprised a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=161), followed by a 1-week, double-blind placebo-controlled phase in which patients were randomized to continue JORNAY PM (n=83) or switched to placebo (n=72) and evaluated in an analogue classroom setting. Study 2 was a 3-week, randomized, double-blind, placebo-controlled, parallel-group study of JORNAY PM (n=81) compared to placebo (n=80) in pediatric patients 6 to 12 years of age.

The information included in this section is based on data from these studies. Adverse reactions were assessed by collecting adverse events (AEs), including elicitation of sleep disturbances, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event (TEAE) of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Serious Adverse Events and Adverse Events Leading to Discontinuation of Treatment

No serious adverse events occurred in either Study 1 or Study 2.

In Study 1, three patients discontinued treatment due to AEs during the open-label treatment phase. The AEs that led to discontinuation included affect lability 0.6% (1/161); agitation and aggression 0.6% (1/161); and anxiety and 2 events of panic attack 0.6% (1/161).

In Study 2, one patient in the JORNAY PM treatment group discontinued from the study due to an AE which was mood swings 1.2% (1/81).

Treatment Emergent Adverse Events Reported in Clinical Trials

TEAEs reported in controlled trials in patients with ADHD treated with JORNAY PM with an incidence greater or equal to 1% are presented in Table 3 and Table 4 for Study 1 and Study 2 respectively.

Table 3: Treatment-Emergent Adverse Events Reported in ≥1% of Children (6 to 12 years of age) with ADHD in a Laboratory Classroom Study with an Open-Label Titration Phase Followed by a 1-week Double-Blind Treatment Phase (Study 1)*

Preferred Term	Open-Label Phase (up to 6 weeks)	Double-Blind Phase (1 week)	
	JORNAY PM n = 161 (%)	JORNAY PM n = 83 (%)	Placebo n = 72 (%)
Psychiatric disorders			
Any Insomnia#	35 (21.7)	5 (6.0)	5 (6.9)
Initial Insomnia	8 (5.0)	4 (4.8)	4 (5.6)
Middle Insomnia	6 (3.7)	0	1 (1.4)
Terminal Insomnia	13 (8.1)	1 (1.2)	0
Affect lability	28 (17.4)	0	0
Irritability	8 (5.0)	0	0
Tic	3 (1.9)	0	0
Agitation	2 (1.2)	0	0
Anxiety	2 (1.2)	0	0
Aggression	1 (0.6)	0	1 (1.4)
Metabolism and nutrition disorders			
Decreased appetite	48 (29.8)	0	0
Increased appetite	3 (1.9)	0	0
Infections and infestations			
Upper respiratory tract infection	20 (12.4)	3 (3.6)	2 (2.8)
Gastroenteritis	4 (2.5)	1 (1.2)	0
Gastroenteritis viral	3 (1.9)	0	1 (1.4)
Otitis media	3 (1.9)	0	0
Conjunctivitis	2 (1.2)	0	0

Preferred Term	Open-Label Phase (up to 6 weeks)	Double-Blind Phase (1 week)	
	JORNAY PM n = 161 (%)	JORNAY PM n = 83 (%)	Placebo n = 72 (%)
Pharyngitis	2 (1.2)	0	0
Sinusitis	2 (1.2)	0	0
Nervous system disorders			
Headache	23 (14.3)	1 (1.2)	1 (1.4)
Dizziness	4 (2.5)	0	0
Gastrointestinal disorders			
Abdominal pain upper	11 (6.8)	0	0
Nausea	7 (4.3)	0	1 (1.4)
Vomiting	7 (4.3)	0	1 (1.4)
Diarrhea	3 (1.9)	0	1 (1.4)
Constipation	2 (1.2)	0	0
Abdominal discomfort	0	1 (1.2)	1 (1.4)
Investigations			
Blood pressure diastolic increased	10 (6.2)	9 (10.8)	7 (9.7)
Weight decreased	5 (3.1)	1 (1.2)	1 (1.4)
Heart rate increased	2 (1.2)	0	0
Blood pressure systolic increased	0	0	1 (1.4)
Injury, poisoning and procedural complications			
Arthropod bite	3 (1.9)	0	0
Radius fracture	2 (1.2)	0	0
Skin abrasion	2 (1.2)	0	0
Ulna fracture	2 (1.2)	0	0
Ligament sprain	0	2 (2.4)	0
Foreign body	0	0	1 (1.4)
Cardiac disorders			
Tachycardia	9 (5.6)	0	1 (1.4)
General disorders and administration site conditions			
Fatigue	2 (1.2)	0	0
Pyrexia	2 (1.2)	1 (1.2)	0
Respiratory, thoracic and mediastinal disorders			
Cough	3 (1.9)	1 (1.2)	1 (1.4)
Oropharyngeal pain	2 (1.2)	0	0
Skin and subcutaneous tissue disorders			

Preferred Term	Open-Label Phase (up to 6 weeks)	Double-Blind Phase (1 week)	
	JORNAY PM n = 161 (%)	JORNAY PM n = 83 (%)	Placebo n = 72 (%)
Dermatitis contact	4 (2.5)	0	0
Renal and urinary disorders			
Enuresis	4 (2.5)	1 (1.2)	1 (1.4)
Ear and labyrinth disorders			
Ear pain	2 (1.2)	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity	2 (1.2)	0	0
Groin pain	0	1 (1.2)	0
Back pain	0	0	1 (1.4)
Neck pain	0	0	1 (1.4)

*Study Duration: up to 7 weeks: Open-Label Phase (flexible dosing from 20 mg to 100 mg), followed by a 1-week, double-blind, placebo-controlled withdrawal phase.

[#]Any insomnia includes TEAEs reported for "insomnia", "initial insomnia", "middle insomnia" and terminal insomnia"

Table 4: **Treatment-Emergent Adverse Events Reported ≥1% of Children (6 to 12 years of age) with ADHD in a 3-Week ADHD Study (Study 2)***

Preferred Term	JORNAY PM n= 81 (%)	Placebo n= 80 (%)
Psychiatric disorders		
Any Insomnia[#]	27 (33.3)	7 (8.8)
Initial Insomnia	11 (13.6)	4 (5.0)
Middle Insomnia	9 (11.1)	3 (3.8)
Terminal Insomnia	9 (11.1)	1 (1.3)
Insomnia	3 (3.7)	1 (1.3)
Affect lability	3 (3.7)	0
Irritability	3 (3.7)	3 (3.8)
Mood swings	2 (2.5)	1 (1.3)
Sleep disorder	2 (2.5)	4 (5.0)
Agitation	1 (1.2)	0
Personality disorder	1 (1.2)	0
Sleep talking	1 (1.2)	0
Somnambulism	1 (1.2)	0

Preferred Term	JORNAY PM n= 81 (%)	Placebo n= 80 (%)
Tic	1 (1.2)	0
Aggression	0	1 (1.3)
Attention deficit/hyperactivity disorder	0	2 (2.5)
Nightmare	0	2 (2.5)
Panic attack	0	1 (1.3)
Gastrointestinal disorders		
Vomiting	7 (8.6)	0
Nausea	5 (6.2)	0
Abdominal pain upper	3 (3.7)	2 (2.5)
Abdominal discomfort	1 (1.2)	0
Diarrhoea	1 (1.2)	0
Gastritis	1 (1.2)	0
Toothache	1 (1.2)	0
Flatulence	0	1 (1.3)
Regurgitation	0	1 (1.3)
Metabolism and nutrition disorders		
Decreased appetite	15 (18.5)	3 (3.8)
Increased appetite	1 (1.2)	0
Nervous system disorders		
Headache	8 (9.9)	4 (5.0)
Psychomotor hyperactivity	4 (4.9)	1 (1.3)
Dizziness	1 (1.2)	1 (1.3)
Dizziness postural	1 (1.2)	0
Lethargy	0	1 (1.3)
Somnolence	0	2 (2.5)
Tremor	0	1 (1.3)
Infections and infestations		
Nasopharyngitis	2 (2.5)	1 (1.3)
Pharyngitis streptococcal	2 (2.5)	0
Gastroenteritis	1 (1.2)	0
Gastroenteritis viral	1 (1.2)	1 (1.3)

Preferred Term	JORNAY PM n= 81 (%)	Placebo n= 80 (%)
Upper respiratory tract infection	1 (1.2)	4 (5.0)
Viraemia	1 (1.2)	0
Viral pharyngitis	1 (1.2)	0
Bronchitis	0	1 (1.3)
Viral upper respiratory tract infection	0	1 (1.3)
Investigations		
Blood pressure diastolic increased	6 (7.4)	3 (3.8)
Heart rate increased	1 (1.2)	1 (1.3)
Weight decreased	1 (1.2)	0
Weight increased	1 (1.2)	0
Alanine aminotransferase increased	0	1 (1.3)
Blood pressure decreased	0	1 (1.3)
Blood pressure systolic increased	0	1 (1.3)
Neutrophil count decreased	0	1 (1.3)
Injury, poisoning and procedural complications		
Contusion	2 (2.5)	0
Ligament sprain	1 (1.2)	0
Muscle strain	1 (1.2)	0
Arthropod bite	0	1 (1.3)
Hand fracture	0	1 (1.3)
Wound	0	1 (1.3)
Skin and subcutaneous tissue disorders		
Rash	2 (2.5)	0
Night sweats	1 (1.2)	0
Ear and labyrinth disorders		
Ear pain	1 (1.2)	0
Tinnitus	1 (1.2)	0
General disorders and administration site conditions		
Fatigue	1 (1.2)	3 (3.8)
Pyrexia	1 (1.2)	1 (1.3)
Peripheral swelling	0	1 (1.3)

Preferred Term	JORNAY PM n= 81 (%)	Placebo n= 80 (%)
Immune system disorders		
Drug hypersensitivity	1 (1.2)	0
Seasonal allergy	1 (1.2)	0
Musculoskeletal and connective tissue disorders		
Back pain	2 (2.5)	0
Blood and lymphatic system disorders		
Neutropenia	1 (1.2)	0
Cardiac disorders		
Tachycardia	1 (1.2)	0
Respiratory, thoracic and mediastinal disorders		
Cough	1 (1.2)	2 (2.5)
Nasal congestion	0	1 (1.3)
Oropharyngeal pain	0	1 (1.3)
Rhinorrhoea	0	1 (1.3)
Sinus congestion	0	2 (2.5)
Renal and urinary disorders		
Enuresis	0	1 (1.3)
Vascular disorders		
Systolic hypertension	0	1 (1.3)

*Study Duration: up to 3 weeks. All participants started at 40 mg/day (half of the participants were randomized to receive placebo). Doses were titrated each week to the next highest dose according to tolerability: 40, 60, and 80 mg/day. Participants were permitted to reduce the dose by one step if necessary for tolerability.

Additional Treatment-Emergent Adverse Events Reported During Clinical Trials with Other Methylphenidate Products

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.

8.3 Less Common Clinical Trial Adverse Reactions

Uncommon TEAEs (incidence less than 1% and not already reported above in the controlled or open label trials)

- **Ear and labyrinth disorders:** Ear swelling
- **Eye disorders:** Astigmatism, Myopia
- **Gastrointestinal disorders:** Dry mouth, Dyspepsia
- **General disorders and administration site conditions:** Feeling abnormal, Feeling jittery
- **Infections and infestations:** Cellulitis, Croup infectious, Ear infection, Nasopharyngitis, Oral herpes, Otitis externa, Pharyngitis streptococcal, Tooth abscess, Viral infection
- **Injury, poisoning and procedural complications:** Animal scratch, Contusion, Excoriation, Head injury, Muscle strain, Periorbital haematoma
- **Musculoskeletal and connective tissue disorders:** Arthralgia, Arthralgia, Fracture pain
- **Psychiatric disorders:** Aggression, Apathy, Blunted affect, Dysphoria, Emotional poverty, Panic attack, Trichotillomania
- **Renal and urinary disorders:** Polyuria, Urinary incontinence
- **Respiratory, thoracic and mediastinal disorders:** Bronchial hyperreactivity
- **Skin and subcutaneous tissue disorders**: Ecchymosis, rash
- **Vascular disorders:** Orthostatic hypotension

8.5 Post-Market Adverse Reactions

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Suicidal Behaviour and Ideation).

Adverse Events Reported with Methylphenidate Hydrochloride Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported.

The following events have also been reported with methylphenidate products: aplastic anemia, pancytopenia, thrombocytopenia, cardiac arrhythmias, ECG QT prolongation, diplopia, increased intraocular pressure, mydriasis, visual impairment, hypoglycemia, muscle cramps,

rhabdomyolysis, choreoathetoid movements, convulsions, dysphemia, presyncope, trismus, change in sustained attention, euphoric mood, hallucinations, impulsive behaviour, logorrhea, obsessive-compulsive disorder, onychophagia, self-injurious behaviour, thinking abnormal, epistaxis, erythema, photosensitivity reaction, skin discoloration, skin odor abnormal, flushing, and vasodilation.

Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, e.g., hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anaemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Co-Administration of Monoamine Oxidase Inhibitors (MAOIs); see 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors • Co-Administration of Clonidine; see 9.4 Drug-Drug Interactions, Clonidine.

9.2 Drug Interactions Overview

Because of possible increases in blood pressure and heart rate, JORNAY PM should be used cautiously with drugs with similar pharmacological actions.

9.3 Drug-Behavioural Interactions

- **Alcohol**
  The concomitant use of alcohol should be avoided (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

  Alcohol may exacerbate the CNS-related adverse effects of psychoactive drugs. Therefore, patients undergoing JORNAY PM therapy should be advised to avoid alcohol during treatment.

  In vitro testing showed that approximately 96% of methylphenidate was released from JORNAY PM capsules in 2 hours in the presence of 40% alcohol. The increase in methylphenidate release rate was not observed in the presence of 5 to 20% alcohol. No *in vivo* studies have been conducted to assess the effect of alcohol on drug exposure.

9.4 Drug-Drug Interactions

- **Inhibition of Drug Metabolism by Methylphenidate**

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of:

- coumarin anticoagulants (e.g., warfarin),
- anticonvulsants (e.g., phenobarbital, phenytoin, primidone) and
- some antidepressants (e.g., tricyclics, SSRIs).

Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times) when initiating or discontinuing concomitant methylphenidate.

- **Monoamine Oxidase Inhibitors:**

  Methylphenidate is contraindicated during treatment with MAOIs and also within a minimum of 14 days following discontinuation of a MAOI (hypertensive crises may result). The same precautions apply to JORNAY PM (see 2 CONTRAINDICATIONS).

- **Clonidine**

  Serious adverse events including sudden death have been reported in concomitant use with clonidine. In these cases, no causality for the combination could be established because of insufficient data.

- **Anti-Hypertensive Drugs**

  Methylphenidate products may decrease the effectiveness of drugs used to treat hypertension. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension and Other Cardiovascular Conditions).

- **Antipsychotics**

  Because a predominant action of methylphenidate is to increase extracellular dopamine levels, JORNAY PM may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both JORNAY PM and an antipsychotic, as extrapyramidal symptoms could emerge when these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.

- **Serotonergic Drugs**

  There have been reports of serotonin toxicity with methylphenidate, including JORNAY PM, with concomitant use of serotonergic drugs. If concomitant treatment with JORNAY PM and other serotonergic agents is clinically warranted, careful observation of the patient is advised (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin toxicity / Serotonin syndrome). If serotonin toxicity is suspected, JORNAY PM (and serotonergic drugs) must be immediately discontinued and appropriate treatment instituted.

- **Halogenated Anesthetics**

  With halogenated anesthetics, there is a risk of sudden blood pressure and heart rate increase during surgery. Methylphenidate may also antagonize the sedative effect of

general anesthetics. If surgery is planned, JORNAY PM should not be taken on the day of surgery.

- **Risperidone**

  The combined use of methylphenidate with risperidone when there is a change in dose of either or both medications may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

9.5 Drug-Food Interactions

There are no known food interactions with JORNAY PM (see 10.3 Pharmacokinetics, Food Effect).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Methylphenidate is a CNS stimulant. The pharmacological properties of methylphenidate are similar to those of the amphetamines. However in contrast to amphetamines, methylphenidate has more prominent effects on mental than motor activities.

The mode of action of stimulants in ADHD is not completely understood, but they are thought to act primarily through indirect mechanisms, such as release of dopamine and norepinephrine from neuronal pools, and inhibition of neurotransmitter reuptake.

Methylphenidate increases extracellular concentrations of dopamine and norepinephrine by inhibiting their neuronal reuptake, and is also an MAO.

The behavioural and cognitive symptoms in ADHD and their response to stimulants are considered to reflect activity of dopaminergic and noradrenergic systems. Dopamine transporter binding sites are increased in the brains of ADHD patients and there is evidence for a genetic basis for this finding. Methylphenidate has been shown to both increase extracellular dopamine in the human brain and to reduce the number of dopamine transporter binding sites in patients with ADHD.

10.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprising the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

JORNAY PM delayed-release and extended-release capsules contain beads with two film coatings (outer delayed-release and inner extended-release) surrounding a methylphenidate hydrochloride drug layered core. Methylphenidate is released at a controlled rate following an initial delay of approximately 8 to 10 hours allowing for once daily oral administration in the evening.

10.3 Pharmacokinetics

Absorption

The pharmacokinetics of methylphenidate after a single, 100 mg oral dose of JORNAY PM administered in the evening at 9 pm were studied in healthy adults. After the lag period, the absorption of methylphenidate occurs in a single peak with a median T_{max} 14.0 hours, followed by a gradual decline throughout the rest of the day.

Figure 1: Arithmetic Mean Plasma Methylphenidate Concentrations following a Single, Oral, 100 mg Dose of JORNAY PM (Methylphenidate Hydrochloride Delayed-Release and Extended-Release Capsule) or Methylphenidate Immediate-Release Oral Product Administered in a Crossover Manner to Healthy Adult Subjects

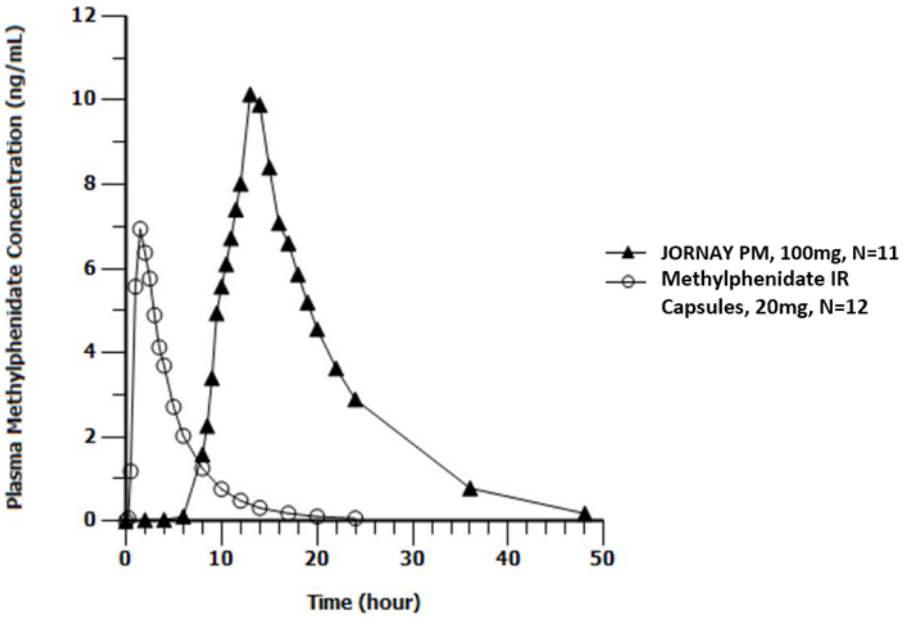


Table 6: Methylphenidate HCl Pharmacokinetic Parameters after Treatment with JORNAY PM

PK Parameter	JORNAY PM, 100 mg N=11
C_{max} (ng/mL), mean (SD)	10.46 (5.64)
AUC_{last} (h·ng/mL), mean (SD)	120 (63.5)
AUC_{inf} (h·ng/mL), mean (SD)	122 (63.8)
T_{max} (h), median (min, max)	14.00 (10.5 – 15.0)
$t_{1/2}$ (h), mean (SD)	6.02 (2.10)

Dose Proportionality

In a single-dose, open-label, crossover study in healthy adults, the pharmacokinetics of methylphenidate was dose-proportional between 20 mg and 100 mg dose level.

Food Effect:

A single-dose, 3-way, crossover study evaluating the PK of 100 mg JORNAY PM in healthy adults (age range 18-55 years) in the fasted state (8 hours), in the fed state (within 30 minutes of a high fat meal), and with the drug capsule contents sprinkled on applesauce (following an 8-hour fast) was completed. Compared to the fasted state, JORNAY PM taken with a high-fat meal at night exhibited similar mean AUC $_{0-\infty}$, a 14% lower mean C_{max}, and a median T_{max} extended by approximately 2.5 hours. After JORNAY PM was taken at night, a morning meal had no effect on the pharmacokinetics of methylphenidate.

The pharmacokinetic parameters were similar when JORNAY PM was taken as a whole capsule or when sprinkled on applesauce. Patients should be advised to take the product consistently with or without food.

Distribution:

In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Methylphenidate and its metabolites exhibit low plasma protein binding (approximately 15%).

Metabolism:

The primary route of metabolism for methylphenidate is de-esterification to the inactive metabolite ritalinic acid (α-phenyl-2-piperidine acetic acid), which represents 60 to 81% of the administered dose, and 6-oxy-α-phenyl-2-piperidineacetic acid (9 to 12% of the administered dose). Unchanged drug accounts for less than 1% of the administered dose. First pass metabolism results in an absolute bioavailability of 30% with large inter-individual differences (11 to 52%).

Elimination:

Methylphenidate is excreted almost entirely in the urine. After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accounting for approximately 80% of the dose (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of methylphenidate after JORNAY PM administration was not studied in pediatric population.
- **Geriatrics:** Specific studies of JORNAY PM in geriatric patients have not been conducted.
- **Pregnancy and Breast-feeding:** 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.
- **Hepatic Insufficiency:** JORNAY PM has not been studied in patients with hepatic insufficiency.
- **Renal Insufficiency:** JORNAY PM has not been studied in patients with renal insufficiency.
- **Obesity:** JORNAY PM has not been studied in patients with obesity.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C to 30°C). Protect from moisture. Keep in a safe place out of the reach and sight of children.

JORNAY PM should be kept in a safe place, such as under lock and out of the sight and reach of children to prevent abuse.

Unused or expired JORNAY PM should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. The patient should speak to their pharmacist about safe disposal.

JORNAY PM should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

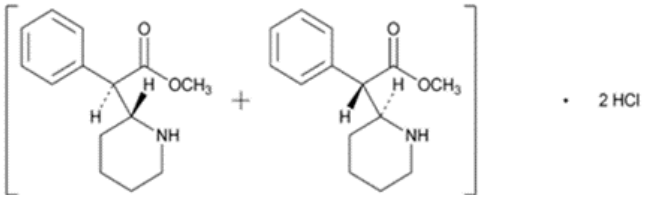
Drug Substance

Proper name: Methylphenidate Hydrochloride USP

Chemical name: 2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride (R*, R*)- (±)-

Molecular formula and molecular mass: $C_{14}H_{19}NO_2 \cdot HCl$; 269.77 g/mol

Structural formula:



Physicochemical properties: Methylphenidate hydrochloride is a white to off-white crystalline powder. The pH of the aqueous solution is acidic to litmus, with a pKa of 8.9-9.0. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. It has a melting point in the range of 224 – 226°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Attention-Deficit Hyperactivity Disorder (ADHD)

The efficacy of JORNAY PM was established in two clinical studies in pediatric patients (male and female) 6 to 12 years of age, with a diagnosis of ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders , Fifth Edition (DSM-5) criteria and confirmation using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

Study 1 included patients with baseline ADHD-RS-IV score at or above the 90th percentile normalized for sex and age in at least 1 of the following categories: Hyperactive–Impulsive, Inattentive, or Total Score and ADHD-RS-IV Total Score ≥26 at Baseline Visit; Clinical Global Impression of Severity (CGI-S) score ≥4 and CGI-P score >10 at Baseline Visit. Study 2 included patients with baseline ADHD-RS-IV score at or above the 90th percentile normalized for sex and age in total score and ADHD-RS-IV Total Score ≥26 at Baseline Visit; Clinical Global Impression of Severity (CGI-S) score ≥4 and CGI-P score >10 at Baseline Visit.

The primary efficacy outcomes in each clinical trial were supported by the secondary endpoints, and data from clinical trials support that once-daily administration of JORNAY PM (dose range 20 to 100 mg/day), taken in the evening, improves efficacy from the early morning, and

throughout the day-based on behavioural (SKAMP , ADHD-RS-IV, PREMB-R AM scores) and functional (BSFQ) measures in children 6-12 years of age.

Table 5 summarizes the patient demographics for Study 1 and Study 2.

Table 5: Summary of Patient Demographics for Pivotal Clinical Trials in Children with ADHD

Study #	Study Design	JORNAY PM Dose/ Treatment Duration	Study Subjects (N)	Mean Age (Range)	Sex	Primary Efficacy Endpoint
Pivotal Trial in Children (6 to 12 years of age)						
Study 1	Double-blind, randomized, placebo-controlled, forced withdrawal, parallel-group in a laboratory classroom setting measuring efficacy and safety; double-blind phase was preceded by an open-label, treatment-optimization phase	Open-label phase: JORNAY PM 20, 40, 60, 80, or 100 mg once daily at 8:00 pm (±1.5 hours) Double-blind phase: Optimal daily dose of JORNAY PM Or placebo Both once daily at 8:00 pm (±1.5 hours)	Dose Optimization Period: JORNAY PM N=161[#] Double-Blind Period N=155* JORNAY PM=83 Placebo=72	9.5 (6-12)	M=97 F=56	SKAMP C score
Study 2	Double-blind, randomized, placebo-controlled, parallel group, multi-center study measuring safety and efficacy	40, 60, or 80 mg or placebo once daily at 8:00 pm (±30 minutes) with adjustments at Visits 3 and 4 (window 6:30 pm to 9:30 pm)	N=163* JORNAY PM= 82 Placebo=81	9.3 (6, 12)	M=113 F=48	ADHD-RS-IV

* All subjects who were randomized and received at least one dose of double-blind study treatment.

[#] All subjects who received at least one dose of open label study drug.

Table 6 summarizes the primary endpoint results for Study 1 and 2.

Table 6: Summary of Primary Efficacy Results in Pediatric Patients (6 –12 years) with ADHD (Studies 1 and 2)

Study Number	Measure (Primary Endpoint)	Treatment Group (# of ITT Subjects)	Mean Baseline Score (SD)	LS Mean (SE)	Placebo-subtracted Difference (95% CI)	p value
Study 1*	**SKAMP CS Average**	JORNAY PM (82)	NA	14.8 (1.03)	-3.6 (-6.4, -0.9)	0.010
		Placebo (71)	NA	18.4 (1.07)		
Study 2	**ADHD-RS-IV**	JORNAY PM (81)	43.1 (7.33)	24.1 (1.50)	-7.0 (-11.4, -2.7)	0.002
		Placebo (80)	43.5 (6.84)	31.2 (1.60)		

ITT: Intent-to-treat. SE: Standard Error. SD: Standard Deviation. CI: Confidence Interval. NA: Not Available. CS: Combined Score (sum of items 1-13)

* Includes data from one study site (n=36) which was deemed unreliable due to data integrity concerns. A similar overall statistical outcome was observed excluding the data (n=36) from that site.

Study 1

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 (n = 161) received JORNAY PM (once each evening; flexible dosing from 20 mg to 100 mg), followed by a 1-week, double-blind, placebo-controlled withdrawal phase in which patients were randomized to continue JORNAY PM (n=82) or switch to placebo (n=71).

After 1 week of double-blind treatment, patients were evaluated in an analog classroom over a 12-hour period using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), a 13-item teacher rated scale that assesses manifestations of ADHD in a classroom setting and each item is rated on a 7-point impairment scale.

The primary efficacy endpoint, the model-adjusted average of all post-dose SKAMP combined scores measured on the laboratory classroom day during the 12-hour analog testing period from 8:00 a.m. to 8:00 p.m, was statistically significantly better (lower) for JORNAY PM compared with placebo (p=0.010) (Table 6). Figure 2 shows the LS mean and standard error of SKAMP combined scores at each of the individual time points from 8:00 a.m. to 8:00 p.m.
The key secondary efficacy endpoint was the morning subscale of the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM), to measure manifestations of ADHD in the early morning. This clinician-rated scale is based on parent interview using three questions and assesses manifestations of ADHD during the early morning period. Possible scores range from 0 (no ADHD manifestations) to 9 (severe ADHD manifestations). The key secondary efficacy endpoint, the PREMB-R AM, was also statistically significantly better (lower) for JORNAY PM versus placebo (p<0.001).

Based on the findings of two independent investigations, data from one study site (n=36) was deemed unreliable due to data integrity concerns; however, post-hoc sensitivity analyses

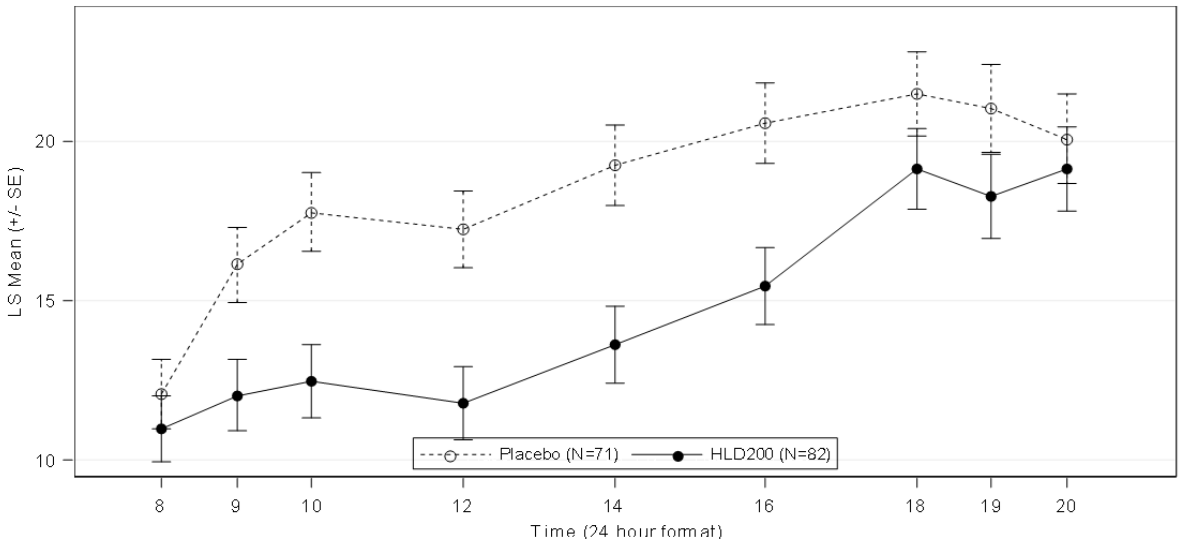
excluding the affected study site did not reveal significant changes on the efficacy and safety outcomes.

Study 2

Study 2 was a 3-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study in pediatric patients, 6 to 12 years of age. Patients were randomized to an evening dose of 40, 60, or 80 mg JORNAY PM (n=81) or placebo (n=80). The primary efficacy endpoint was the ADHD Rating Scale (ADHD-RS-IV) Total Score, measuring severity of manifestations throughout the day. A key secondary efficacy endpoint was the Before School Functioning Questionnaire (BSFQ), a clinician-rated 20-item questionnaire assessing ADHD manifestations on a severity scale of 0 to 3 for early morning before school activities from the time the child awakens and some behaviors not specific to early morning.

After 3 weeks of treatment, the ADHD-RS-IV total score was statistically significantly better (lower) for JORNAY PM than placebo (p=0.002) (Table 6). The key secondary efficacy endpoint, the BSFQ, was statistically significantly better (lower) for JORNAY PM versus placebo (p<0.001).

Figure 2: Study 1 - Least Squares Mean SKAMP Combined Score over 12 hours on day after final treatment, as measured in a analogue classroom in pediatric patients (6 to 12 years old) with ADHD (N=153)*



SE: Standard Error; SKAMP CS = Swanson, Kotkin, Agler, M-Flynn, and Pelham combined score
The SKAMP CS was obtained from the sum of items 1-13, with each item being rated on a 7-point scale (0 = normal to 6 = maximal impairment).
Treatment comparisons were assessed using a mixed-effects model of repeated measures analysis, with treatment (HLD200/placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect.
* Includes data from one study site (n=36) which was deemed unreliable due to data integrity concerns. A similar overall statistical outcome was observed excluding the data (n=36) from that site.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Genotoxicity:

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or in the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Carcinogenicity:

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 1.5 times the maximum recommended human dose of 100 mg/day given to children on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 2 times the maximum recommended human dose (children) on a mg/m^2 basis.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Reproductive and Developmental Toxicology:

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18 week continuous breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 6-times the maximum recommended human dose of 100 mg/day given to adolescents on a mg/m^2 basis.

No teratogenic effects were observed in rats when given at a dose of 75 mg/kg/day, which is approximately 23 and 3.75 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. However, methylphenidate was shown to be teratogenic in rabbits when given at a dose of 200 mg/kg/day, which is approximately 62.5 times and 20 times higher than the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Juvenile Toxicity:
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 maximum recommended human dose 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 ≥ 50 mg/kg/day (approximately ≥ 2.5 times the maximum recommended human dose on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (approximately 5 times the maximum recommended human dose 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 maximum recommended human dose on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

JORNAY PM®

Methylphenidate Hydrochloride Delayed-Release and Extended-Release Capsules

Read this carefully before you start taking **JORNAY PM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JORNAY PM**.

Serious Warnings and Precautions

Drug Dependence

Like other stimulants, JORNAY PM has the potential to be abused. This can lead to you becoming dependent on JORNAY PM or feeling like you need to take more of it over time.

What is JORNAY PM used for?

JORNAY PM is a once-daily treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children 6 to 12 years of age.

JORNAY PM is NOT recommended for use in children under 6 years of age.

The child's healthcare professional may include as part of their treatment with JORNAY PM, other measures such as psychological counselling, educational and social measures, as part of their total treatment program.

How does JORNAY PM work?

JORNAY PM belongs to a group of medicines called central nervous system stimulants. The way JORNAY PM works in the brain is not completely known. JORNAY PM helps increase attention and decreases impulsiveness and hyperactivity in patients with ADHD. It is designed to be taken as a single dose in the evening to help symptoms of ADHD by delivering the active ingredient, methylphenidate hydrochloride, to the bloodstream, both in the morning and later in the day.

What are the ingredients in JORNAY PM?

Medicinal ingredient: methylphenidate hydrochloride

Non-medicinal ingredients: dibutyl sebacate, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, mono- and di-glycerides, polysorbate 80, and talc.

In addition, the capsule shells contain the following non-medicinal ingredients:

- 20 mg: FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint.

- 40 mg: FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint.
- 60 mg: FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint.
- 80 mg: FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint.
- 100 mg: black iron oxide, FD&C Blue#1, hypromellose, red iron oxide, titanium dioxide, black ink, and white ink for the imprint.

JORNAY PM comes in the following dosage forms:

Delayed-release and extended-release capsules: 20 mg, 40 mg, 60 mg, 80 mg and 100 mg

Do not use JORNAY PM if the child:

- is allergic to methylphenidate hydrochloride, to any other central nervous system stimulants, or any of the ingredients in JORNAY PM
- has ever had heart problems such as a heart attack, irregular heartbeat, chest pain (angina), heart failure, heart disease or were born with a heart problem
- has moderate to severe high blood pressure (hypertension)
- has hardened arteries (arteriosclerosis)
- has an overactive thyroid gland
- has significant anxiety, tension, or agitation
- has increased eye pressure (glaucoma)
- has, or there is a family history of Tourette's syndrome, including uncontrolled speech (verbal tics) and body movements (motion tics)
- is taking or have taken within the last 14 days, a medicine from a group called monoamine oxidase inhibitors (MAOI)
- has a condition called pheochromocytoma (a rare tumour that usually grows in the adrenal glands, above the kidneys)
- has a history of drug abuse or is showing interest in drugs

To help avoid side effects and ensure proper use, talk to the child's healthcare professional before they take JORNAY PM. Talk about any health conditions or problems they may have, including if the child:

- has heart problems, heart defects, or mild high blood pressure
- has an abnormal heart rate or rhythm
- has a family history of sudden death or death related to heart problems
- has any other current or previous heart problems
- does strenuous exercise
- take other stimulant drugs
- is showing an interest in drinking alcohol, is drinking alcohol or has a history of alcohol abuse. The child should not drink alcohol while taking JORNAY PM
- has had seizures or abnormal EEGs (measure of brainwave activity)
- has or has had any disorder of the blood vessels in the brain such as weakening of blood vessels (aneurysm), stroke, inflammation of blood vessels (vasculitis)

- has mental problems or family history of mental health problems including psychosis, mania, suicide, bipolar illness, depression, anxiety or aggression
- is pregnant or plans to become pregnant
- is breastfeeding or plans to breastfeed. JORNAY PM passes into breast milk. Talk to the child's healthcare professional to determine if they should stop breastfeeding or stop taking JORNAY PM
- is farsighted (objects in the distance are seen clearly but objects nearby may be blurry)

Other warnings you should know about:

Driving and using machines: JORNAY PM can affect the child's ability to perform certain tasks such as driving and using tools or machinery. They should not do these tasks until they know how they respond to JORNAY PM.

Dependence and tolerance: Like other stimulants, JORNAY PM has the potential to be abused if not taken correctly which can lead to dependence and tolerance. If the child has a history of drug or alcohol abuse, discuss this with their healthcare professional. DO NOT change the dose or stop taking JORNAY PM without first discussing this with their healthcare professional. If the child stops taking JORNAY PM, they will need careful supervision because they may feel very depressed.

Growth in children: Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate hydrochloride in children. The child's healthcare professional will carefully watch their height and weight. If the child is not growing or gaining weight as expected, their healthcare professional may stop treatment.

Heart Related Problems: The following heart related problems have been reported in people taking medicine to treat ADHD like JORNAY PM:

- sudden death in patients who have heart problems or heart defects
- stroke and heart attack in adults
- increased blood pressure and heart rate.

Sudden death has been reported with drugs used for ADHD treatment in children/adolescents with structural heart abnormalities or other serious heart problems. Although some serious heart problems alone can carry an increased risk of sudden death, JORNAY PM generally should not be used in children, adolescents or adults with known structural heart abnormalities or other serious heart disease or conditions.

Tell the child's healthcare provider if they have any heart problems, heart defects, high blood pressure or a family history of these problems.

The child's healthcare professional will check:

- for heart problems before starting JORNAY PM
- blood pressure and heart rate regularly during treatment with JORNAY PM

Get medical help right away if the child has any signs of heart problems such as chest pain, difficulty breathing or fainting while taking JORNAY PM.

Mental health problems: The following mental health problems have been reported in people taking medicine to treat ADHD like JORNAY PM:

- new and worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, suicidal ideation and completed suicide)
- new or worse bipolar illness (extreme mood swings, with periods of excitement, switching between periods of sadness)
- new or worse aggressive behaviour or hostility, anxiety or feeling agitated
- new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real, being suspicious) or new manic symptoms

These new or worse mental health problems may be more likely to occur if the child has mental health conditions that you may or may not know about. Tell their healthcare professional about any mental problems they have, or about any personal or family history of suicide, bipolar illness, or depression.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time during treatment, particularly at the start or during dose changes, and also after stopping JORNAY PM. **Should this happen, consult the child's healthcare professional immediately. Close observation by a healthcare professional is necessary in this situation.**

Raynaud's phenomenon: Stimulants used to treat ADHD, such as JORNAY PM, are associated with Raynaud's Phenomenon. During treatment with JORNAY PM, the child's healthcare professional may check for problems with the circulation in their fingers and toes, including numbness, feeling cold or pain.

Serotonin toxicity (also known as Serotonin Syndrome): JORNAY PM can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how the child's brain, muscles and digestive system work. They may develop serotonin toxicity if they take JORNAY PM with certain anti-depressants or migraine medications. Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination
- fast heartbeat, changes in blood pressure
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma

Testing and check-ups: The healthcare professional may do tests before the child starts treatment with JORNAY PM and during their treatment. These tests may include:

- tests that check for problems in the heart or brain
- tests that check your blood pressure and heart rate
- blood tests to check complete blood count, platelet counts and liver enzymes

Tell your healthcare professional about all the medicines the child takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
The child MUST NOT take JORNAY PM if they: • are taking or have recently taken (within the last 14 days) any MAOIs such as phenelzine, tranylcypromine, or moclobemide as you may have serious side effects. • are taking clonidine (used to treat high blood pressure). It may cause serious side effects including sudden death.

The following may interact with JORNAY PM:

- alcohol. The child should avoid drinking alcohol, including any medication containing alcohol, such as some cough syrups, while taking JORNAY PM
- certain medicines for depression or anxiety called tricyclic antidepressants, 'selective serotonin reuptake inhibitors' (SSRIs) or 'serotonin and norepinephrine reuptake inhibitors' (SNRIs)
- medicines used to manage psychosis (antipsychotic)
- medicines used to prevent seizures such as phenobarbitone, phenytoin, and primidone;
- medicines used to prevent blood clots (commonly called "blood thinners"), such as warfarin
- medicines used to increase blood pressure
- medicines used to treat high blood pressure
- anesthetics on the day of an operation, as there is a chance of a sudden rise in blood pressure and heart rate during the operation
- risperidone, used to treat the symptoms of schizophrenia and related psychotic disorders

How to take JORNAY PM:

- The child's healthcare professional will decide on the dose that is right for them. Always follow the directions of the healthcare professional and never change the dose or stop taking JORNAY PM without first discussing it with the child's healthcare professional.
- Take JORNAY PM once a day, in the evening. It should be taken at the same time each evening.
- JORNAY PM can be taken with or without food but should be taken the same way each time.
- Swallow JORNAY PM capsules whole.
- If the child is unable to swallow the capsules whole, the capsules may be opened and the entire contents sprinkled onto applesauce.
    - swallow **all** the applesauce and medicine mixture right away
    - **do not** chew the applesauce and medicine mixture
    - **do not** store the applesauce and medicine mixture

Usual dose:

Children (6-12 years of age):

- Take JORNAY PM exactly as prescribed by the child's healthcare professional.
- The child's healthcare professional will determine the best dose to treat their symptoms and may adjust the dose until it is right.
- From time to time the child's healthcare professional may sometimes interrupt their JORNAY PM treatment to check for symptoms while the child is not taking the medicine.

Overdose:

If you think the child, or a person you are caring for, have taken too much JORNAY PM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If the child forgets to take their dose at the usual time, they should take it as soon as they remember in the same evening. If they do not remember until the next day, they should not take the missed dose. Do not take a morning or afternoon dose. Wait until the evening and take the usual dose at the usual time. Do not double the dose to make up for the missed dose.

What are possible side effects from using JORNAY PM?

These are not all the possible side effects the child may have when taking JORNAY PM. If the child experiences any side effects not listed here, tell their healthcare professional.

Side effects may include:

- sore throat, cough and runny nose
- decreased appetite
- trouble sleeping
- sleep talking, sleepwalking
- nausea, dry mouth
- trembling
- headache, dizziness,
- feeling drowsy, tired or sleepy
- diarrhea, constipation, vomiting,
- indigestion, stomach pain
- muscle, back, or joint pain
- bedwetting in children during the night (enuresis)
- weight loss
- lack of bladder control (incontinence)
- feeling jittery, nervous, anxious or irritable
- increased sweating, night sweats
- ear ringing, ear pain

- vertigo
- swelling of the breasts in boys or men
- difficulty opening the mouth (trismus)
- double vision
- stuttering

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Dyskinesia: uncontrollable twitching and jerking			✓
Heart problems: fast or uneven heartbeat, chest pain, difficulty breathing, fainting			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in the ankles and legs, bluish colour to the lips and skin, racing pulse or fast or uneven heartbeat	✓		
Raynaud's Phenomenon (episodes of reduced blood flow): cold feeling in fingers and toes (and sometimes nose, lips and ears), prickly or stinging feeling, change in skin colour to white then blue			✓
RARE			
Blurred vision		✓	
VERY RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Cerebrovascular disorders (problems with the blood vessels in the brain): severe headaches, weakness or paralysis of any body part, or problems with coordination, vision, speaking, finding words or with your memory, stroke			✓
Choreoathetoid movements: uncontrollable writhing movements of the limb, face and/or trunk		✓	
Erythema multiforme: red blotches on the skin		✓	
Exfoliative dermatitis: skin blisters or itching			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hallucinations: seeing or feeling things that are not really there			✓
Leukopenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms	✓		
Muscle twitching or tics	✓		
Neuroleptic Malignant Syndrome: pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓
Seizures (fits): uncontrollable shaking with or without loss of consciousness			✓
Thrombocytopenic purpura: bleeding under the skin, bruising		✓	
UNKNOWN			
Aggressive Behaviour or Hostility		✓	
Glaucoma (increased pressure in the eye): eye and head pain, swelling or redness in or around the eye, and changes in vision, hazy or blurred vision, sudden sight loss		✓	
New or worsening mental health problems: paranoia, delusions, hallucinations (seeing, feeling or hearing things that are not there), mania (feeling unusually excited, over-active, or uninhibited)		✓	
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Rhabdomyolysis (breakdown of damaged muscle): muscle weakness, muscle pain, muscle spasms, red-brown coloured urine		✓	
Suicidal Behaviour: thoughts or actions about hurting or killing yourself (including completed suicide).			✓
Tourette's Syndrome: motor tics (hard-to-control, repeated twitching of any part of your body) and verbal tics (hard-to-control repeating of sounds or words)			✓

If the child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with their daily activities, tell their healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C). Protect from moisture.
- Keep unused or expired JORNAY PM in a secure place to prevent theft, misuse or accidental exposure.
- Keep JORNAY PM out of sight and reach of children and pets.
- JORNAY PM should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about JORNAY PM:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://ironshorepharma.com, or by calling 1-855-331-5615.

This leaflet was prepared by Ironshore Pharmaceuticals & Development, Inc.

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