PRODUCT MONOGRAPH

◈pms-METHYLPHENIDATE
Methylphenidate Hydrochloride Tablets, USP
5 mg, 10 mg, and 20 mg

Central Nervous System Stimulant

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THERAPEUTIC CLASSIFICATION

Central Nervous System Stimulant

ACTION AND CLINICAL PHARMACOLOGY

pms-METHYLPHENIDATE (Methylphenidate Hydrochloride Tablets) is a racemate consisting of a 1:1 mixture of d-methylphenidate (d-MPH) and l-methylphenidate (l-MPH).

pms-METHYLPHENIDATE is a mild central nervous system stimulant with more prominent effects on mental than motor activities.

The mode of action in man is not completely understood, but its stimulant effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system.

There is neither specific evidence, which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioural effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system (CNS).

Pharmacokinetics

Absorption
Methylphenidate hydrochloride is rapidly and extensively absorbed from the tablets following oral administration; however, owing to extensive first-pass metabolism, bioavailability is low (approx. 30%) and large individual differences exist (11-52%). In one study, the administration of methylphenidate hydrochloride with food accelerated absorption, but had no effect on the amount absorbed.

Distribution
Peak plasma concentrations of 10.8 and 7.8 ng/mL were observed, on average, 2 hours after administration of 0.30 mg/kg in children and adults, respectively. Peak plasma concentrations showed marked variability between subjects. Both the area under the concentration-time curve (AUC), and the peak plasma concentrations (Cmax) showed dose-proportionality.

Elimination
Methylphenidate is eliminated from the plasma with a mean half-life of 2.4 hours in children and 2.1 hours in adults. The apparent mean systemic clearance after an oral dose is 10.2 and

10.5 L/h/kg in children and adults, respectively for a 0.3 mg/kg dose, and 0.565 L/h/kg after an intravenous dose of the racemate in healthy adult volunteers. These data indicate that the pharmacokinetics of methylphenidate in hyperactive children is similar to that in healthy adult volunteers. The apparent distribution volume of methylphenidate in children was approximately 20 L/kg, with substantial variability (11-33 L/kg). The volume of distribution after an intravenous dose (Vss) is 2.23 L/kg for the racemate in healthy adult volunteers.

Following oral administration of methylphenidate, 78-97% of the dose is excreted in the urine and 1-3% in the feces in the form of metabolites within 48-96 hours. The main urinary metabolite is ritalinic acid (a-phenyl-2-piperidine acetic acid, PPAA); unchanged methylphenidate is excreted in the urine in small quantities (< 1%). Peak PPAA plasma concentrations occurred at approximately the same time as peak methylphenidate concentrations, however, levels were several-fold greater than those of the unchanged drug. The half-life of PPAA was approximately twice that of methylphenidate.

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

Methylphenidate excretion into breast milk has been noted in two case reports, where the calculated relative infant dose was ≤ 0.2% of the weight adjusted maternal dose.

Comparative Bioavailability Studies

A randomized, double blinded, two-treatment, two-period, two-sequence, single oral dose (2 x 10 mg), crossover comparative bioavailability study of pms-METHYLPHENIDATE tablets 10 mg (Pharmascience Inc.) and RITALIN® tablets 10 mg (Ciba-Geigy Canada Ltd.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Methylphenidate (2 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	53.51 54.95 (23.5)	52.11 53.48 (23.7)	102.7	99.4 – 106.1
AUC (ng·h/mL)	55.48 57.09 (24.3)	54.17 55.73 (24.8)	102.4	99.1 – 105.9
C_{max} (ng/mL)	11.63 11.99 (26.1)	11.07 11.33 (23.7)	105.0	99.6 – 110.7
T_{max}[3] (h)	1.70 (27.8)	1.80 (25.9)		
$T_{½}$[3] (h)	2.68 (14.6)	2.66 (13.4)		

[1] pms-METHYLPHENIDATE (methylphenidate hydrochloride) tablets, 10 mg (Pharmascience Inc)
[2] RITALIN® (methylphenidate hydrochloride) tablets, 10 mg (Ciba-Geigy Canada Ltd.)
[3] Express as the arithmetic mean (CV %) only

INDICATION AND CLINICAL USE

pms-METHYLPHENIDATE is indicated for the treatment of:

- **Attention Deficit Hyperactivity Disorder (ADHD)**

Need for Comprehensive Treatment Program

pms-METHYLPHENIDATE 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 healthcare professional's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of Methylphenidate Hydrochloride Tablets for long-term use, i.e. for more than 4 weeks has not been systematically evaluated in placebo-controlled trials. Therefore, the healthcare professional who elects to use pms-METHYLPHENIDATE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

- **Narcolepsy**

Pediatrics

Pediatrics (6-18 years of age): see DOSAGE AND ADMINISTRATION, Children and Adolescents (6 Years and Over).

Pediatrics (<6 years of age): pms-METHYLPHENIDATE should not be used in children under 6 years of age (see DOSAGE AND ADMINISTRATION, Dosing Considerations; WARNINGS, Use in Children Under Six Years of Age).

Geriatrics

Geriatrics (>60 years of age): No studies have been performed in patients over 60 years of age; therefore, the safety and efficacy in this population has not been established.

CONTRAINDICATIONS

pms-METHYLPHENIDATE is contraindicated in the following conditions:

- Known or suspected hypersensitivity to the drug or to any of its excipients. For a complete listing, see the COMPOSITION section of the Product Monograph.
- Anxiety, tension
- Agitation
- Thyrotoxicosis
- Advanced arteriosclerosis
- Pre-existing cardiovascular disorders including moderate to severe hypertension, angina, arterial occlusive disease; heart failure, hemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). See WARNINGS, Cardiovascular
- Glaucoma
- Pheochromocytoma
- Patients with motor tics and/or family history or diagnosis of Tourette's syndrome. See WARNINGS, Tics.
- During treatment with monoamine oxidase (MAO) inhibitors, and/or within a minimum of 14 days following discontinuation of those drugs, due to risk of hypertensive crises. See DRUG INTERACTIONS, Use with Drugs That Elevate Blood Pressure.

WARNINGS

Serious Warnings and Precautions

Drug Dependence – Like other stimulants, pms-METHYLPHENIDATE has the potential to be abused, leading to dependence and tolerance (see WARNINGS, Dependence/Tolerance)

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, pms-METHYLPHENIDATE generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities (e.g., cardiomyopathy, serious heart rhythm abnormalities) or other serious cardiac problems that may increase vulnerability to the sympathomimetic effects of a stimulant drug.

Adults
Sudden deaths, 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 such as 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 CONTRAINDICATIONS, Pre-existing Cardiovascular Disorders).

General
Children: 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.

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 ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of 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 judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram 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.

Misuse and Cardiovascular Events
Misuse of stimulants of the CNS, including pms-METHYLPHENIDATE, may be associated with sudden death and other serious cardiovascular adverse events.

Hypertension and other Cardiovascular Conditions
pms-METHYLPHENIDATE is contraindicated in patients with moderate to severe hypertension. Sympathomimetic medications can cause a modest increase in average blood pressure and average heart rate and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is 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 (see CONTRAINDICATIONS, Pre-existing Cardiovascular Disorders).

Cerebrovascular

Cerebrovascular Conditions
Patients with pre-existing CNS abnormalities, e.g., cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with pms-METHYLPHENIDATE. Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with pms-METHYLPHENIDATE (see above, WARNINGS, Cardiovascular, and, DRUG INTERACTIONS, Use with Drugs That Elevate Blood Pressure).

Dependence/Tolerance

Drug Dependence: pms-METHYLPHENIDATE contains methylphenidate, a Schedule III Controlled Substance. Like other stimulants, pms-METHYLPHENIDATE has the potential for abuse and long-term use can lead to the development of tolerance. pms-METHYLPHENIDATE should be given cautiously, particularly to those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative (see WARNINGS, Serious Warnings and Precautions).

Chronically abusive use 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 drug withdrawal, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of an underlying disorder that may require follow-up.

Clinical data indicate that treatment with Methylphenidate Hydrochloride Tablets during childhood and/or adolescence does not seem to result in increased predisposition for addiction.

Endocrine and Metabolism

Long-Term Suppression of Growth
Suppression of growth (i.e., weight gain and/or height) has been reported with the long-term use of stimulants, including Methylphenidate Hydrochloride Tablets, in children (see ADVERSE REACTIONS). Growth should be monitored as clinically necessary during treatment with pms-METHYLPHENIDATE, and patients who are not growing or gaining height or weight as

expected may need to have their treatment interrupted. In addition, the use of "Drug Holidays" is recommended, that is, withholding the drug on weekends and during school holidays inasmuch as the clinical situation permits.

Lactose
pms-METHYLPHENIDATE contains lactose. Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

Fatigue

pms-METHYLPHENIDATE should not be used for the prevention or treatment of normal fatigue states.

Neurologic

Seizures
There is some clinical evidence that Methylphenidate Hydrochloride Tablets may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in 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 Hydrochloride Tablets. If seizure frequency rises, the drug should be discontinued.

Serotonin Toxicity / Serotonin Syndrome
Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition that has been reported during the combined use of methylphenidate with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (see DRUG INTERACTIONS, Use with Serotonergic Drugs). Other common serotonergic drugs include: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs); see CONTRAINDICATIONS, During treatment with monoamine oxidase (MAO) inhibitors), serotonin 5-HT1 receptor agonists (triptans), and 5-HT3 receptor antagonist antiemetics.

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 pms-METHYLPHENIDATE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment

initiation and dose increases (see DRUG INTERACTIONS, Use with Serotonergic Drugs). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Tics
Methylphenidate Hydrochloride Tablets are associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see ADVERSE REACTIONS). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate for ADHD treatment. pms-METHYLPHENIDATE is contraindicated in case of diagnosis or family history of Tourette's syndrome (see CONTRAINDICATIONS, Motor tics and/or Tourette's syndrome). Patients should be regularly monitored for the emergence or worsening of tics during treatment with pms-METHYLPHENIDATE.

Ophthalmologic

Visual Disturbance
Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Psychiatric Conditions

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with pms-METHYLPHENIDATE, patients should be assessed for pre-existing and/or a family history of psychiatric disorders (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Treatment of ADHD with stimulant products including pms-METHYLPHENIDATE should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered.

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
Aggressive behaviour or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour or hostility.

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, patients and healthcare professional's 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 healthcare professional should initiate appropriate treatment of any underlying psychiatric condition and consider a possible discontinuation or change in the ADHD treatment (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Depression
pms-METHYLPHENIDATE should not be used to treat severe exogenous or endogenous depression.

Sexual Function/Reproduction

Priapism
Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products, including Methylphenidate Hydrochloride Tablets in both pediatric and adult patients (see ADVERSE REACTIONS, Post-Market Adverse Drug 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.

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants used to treat ADHD, such as pms-METHYLPHENIDATE, 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.

Special populations

Pregnant Women

There is limited experience with use of methylphenidate in pregnant women. Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day.

Cases of neonatal cardiorespiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous reports.

Therefore, pms-METHYLPHENIDATE should not be given to pregnant women unless the potential benefit outweighs the risk to fetus.

Nursing Women

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

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 pms-METHYLPHENIDATE therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Use in Children Under Six Years of Age

pms-METHYLPHENIDATE should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

PRECAUTIONS

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

Drug treatment is not indicated in all cases of ADHD and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe pms-METHYLPHENIDATE should depend on the healthcare professional's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription 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 pms-METHYLPHENIDATE is usually not indicated.

Hematological Effects

Long-term effects of Methylphenidate Hydrochloride Tablets in children have not been well-established.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy. In the event of hematological disorders appropriate medical intervention should be considered (see ADVERSE REACTIONS).

Driving and Using Machines

pms-METHYLPHENIDATE may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see ADVERSE REACTIONS). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

DRUG INTERACTIONS

Pharmacodynamic Interactions

Anti-hypertensive Drugs
pms-METHYLPHENIDATE may decrease the effectiveness of drugs used to treat hypertension.

Use with Drugs That Elevate Blood Pressure
Use with caution in patients being treated with drugs that elevate blood pressure (see also WARNINGS, Cerebrovascular Conditions).

Because of possible hypertensive crisis, pms-METHYLPHENIDATE is contraindicated in patients being treated (currently or within the preceding 14 days) with MAO-inhibitors (see CONTRAINDICATIONS, MAO inhibitors).

Use with 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, pms-METHYLPHENIDATE should not be taken on the day of surgery.

Use with Centrally Acting Alpha-2 Agonists (e.g., 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.

Use with Dopaminergic Drugs
As an inhibitor of dopamine reuptake, pms-METHYLPHENIDATE may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA [3,4-dihydroxephenylalanine] and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g., haloperidol). Concomitant use of pms-METHYLPHENIDATE with antipsychotics is not recommended due to its counteracting mechanism of action. If upon medical assessment the combination is deemed necessary, monitoring for extrapyramidal symptoms (EPS) is warranted as the concomitant use of methylphenidate with antipsychotics may increase the risk of EPS when there is a change (increase or decrease) in dosage of either or both medications.

Use with Alcohol
Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including pms-METHYLPHENIDATE. Therefore, patients should be advised to abstain from alcohol during treatment

Use with Serotonergic Drugs
The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin toxicity (see WARNINGS, Serotonin Toxicity/Serotonin Syndrome). Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic Interactions

Methylphenidate Hydrochloride Tablets are not metabolized by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on Methylphenidate Hydrochloride Tablets pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate in Methylphenidate Hydrochloride Tablets did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Methylphenidate Hydrochloride Tablets co-administration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports suggested a potential interaction of methylphenidate hydrochloride with coumarin anticoagulants, some anticonvulsants (e.g., phenobarbital, diphenylhydantoin, primidone), phenylbutazone and tricyclic antidepressants but pharmacokinetic interactions were not

confirmed when explored at larger sample sizes. Downward dosage adjustments of these drugs might be required when given concomitantly with pms-METHYLPHENIDATE.

An interaction with the anticoagulant ethylbiscoumacetate in 4 subjects was not confirmed in a subsequent study with a larger sample size (n=12).

Other specific drug-drug interaction studies with Methylphenidate Hydrochloride Tablets have not been performed *in vivo*.

Drug-laboratory Test

Methylphenidate may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

ADVERSE REACTIONS

Adverse drug reactions are listed by MedDRA-based system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category is based on the following convention (CIOMS III): very common ≥10 %, common ≥ 1% to < 10%; uncommon ≥ 0.1 % to < 1%; rare ≥ 0.01% to < 0.1 %; very rare < 0.01 %.

Nervousness and insomnia are very common adverse reactions which occur at the beginning of pms-METHYLPHENIDATE (Methylphenidate Hydrochloride Tablets) treatment, but can usually be controlled by reducing dosage and/or omitting the afternoon or evening dose.

Decreased appetite is also very common but usually transient. Abdominal pain, nausea and vomiting are common to very common, usually occur at the beginning of treatment and may be alleviated by concomitant food intake.

Blood and the Lymphatic System Disorders
Very rare: leucopenia, thrombocytopenia, anemia.

Cardiac Disorders
Common: palpitations, changes in blood pressure and heart rate (usually an increase), tachycardia, cardiac arrhythmias.

Rare: angina pectoris.

Central and Peripheral Nervous System Disorders
Common: dyskinesia, tremor, headache, drowsiness, dizziness.

Very rare: convulsions, choreoathetoid movements, tics, or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral hemorrhages and cerebrovascular accidents.

Eye Disorders
Rare: Symptoms of visual disturbances, difficulties in visual accommodation and blurred vision.

Gastrointestinal Disorders
Very common: nausea, dry mouth.

Common: abdominal pain, vomiting, dyspepsia, toothache.

General Disorders and Administration Site Conditions
Common: feeling jittery.

Rare: slight growth retardation during prolonged use in children.

Hepatobiliary Disorders
Very rare: abnormal liver function, ranging from transaminase elevation to hepatic coma.

Immune System Disorders
Very rare: hypersensitivity reactions, including angioedema and anaphylaxis.

Infections and Infestations
Very common: nasopharyngitis.

Investigations
Common: weight decreased.

In children, loss of appetite, abdominal pain, weight decrease, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

Very rare: neuroleptic malignant syndrome (NMS). Reports of poorly documented NMS have been received. In most of these reports, patients were also receiving other medications. It is uncertain what role Methylphenidate Hydrochloride Tablets played in these cases.

Metabolism and Nutrition Disorders
Very common: decreased appetite.

Rare: moderately reduced weight gain during prolonged use in children.

Musculoskeletal and Connective Tissue Disorders
Common: arthralgia.

Very rare: muscle cramps.

Psychiatric Disorders
Very common: nervousness, insomnia.

Common: anxiety, restlessness, sleep disorder, agitation.

Very rare: hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood.

Respiratory, Thoracic and Mediastinal Disorders
Common: cough.

Skin and Subcutaneous Tissue Disorders
Common: rash, pruritus, urticaria, fever, scalp hair loss, hyperhidrosis.

Very rare: exfoliative dermatitis, erythema multiforme, thrombocytopenic purpura.

Post-Market Adverse Drug Reactions

Blood and the Lymphatic System Disorders
Aplastic anaemia, Transient pancytopenia.

Gastrointestinal Disorders
Pancreatitis.

General Disorders and Administration Site Conditions:
Sudden cardiac death.

Immune System Disorders
Stevens-Johnson Syndrome.

Metabolism and nutrition disorders
Hypoglycaemia.

Musculoskeletal and Connective Tissue Disorders
Trismus

Psychiatric Disorders
Dysphemia, depression, aggression, bruxism

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 WARNINGS, Suicidal Behaviour and Ideation)

Renal and Urinary Disorders
Enuresis

Reproductive System and Breast Disorders
Priapism: Priapism has been reported with methylphenidate products, including RITALIN (see WARNINGS, Priapism).

Vascular Disorders
Peripheral coldness, Raynaud's phenomenon.

Adverse Events with Other Methylphenidate Hydrochloride Products

In addition to the adverse events listed above for Methylphenidate Hydrochloride Tablets the following have been reported with other 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. 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 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.

The list below shows adverse reactions that have been reported with other methylphenidate-containing products based on clinical trials data and post-marketing spontaneous reports:

Cardiac Disorders: Cardiac arrest, myocardial infarction.

Eye Disorders: Diplopia, mydriasis.

Gastrointestinal Disorders: Diarrhea, constipation.

General Disorders and Administration Site Conditions: Chest pain, fatigue.

Investigations: Cardiac murmur.

Musculoskeletal, Connective Tissue Disorders: Myalgia, muscle twitching, rhabdomyolysis.

Nervous System Disorders: Reversible ischemic neurological deficit, migraine.

Psychiatric Disorders: Irritability, affect lability, abnormal behaviour or thinking, anger, mood altered, mood swings, hypervigilance, mania, disorientation, libido disorder, apathy, repetitive behaviours, over-focusing, confusional state, dependence, cases of abuse and dependence have been described, more often with immediate release formulations.

Renal and Urinary Disorders: Hematuria.

Reproductive System and Breast Disorders: Gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal pain, dyspnea.

Skin and Subcutaneous Tissue Disorders: Angioneurotic oedema, erythema, fixed drug eruption.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Management consists in providing supportive measures, and symptomatic treatment of life-threatening events, e.g., hypertensive crisis, cardiac arrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the practitioner should consult a certified Poison Control Center or current toxicological publication.

Supporting measures include preventing self-injury and protecting the patient from external stimuli that would exacerbate the overstimulation already present. If the overdose is oral and the patient is conscious, gastric contents could be evacuated by induction of emesis, followed by administration of activated charcoal.

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 Hydrochloride Tablets overdosage has not been established.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

pms-METHYLPHENIDATE 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 methylphenidate varies widely.

pms-METHYLPHENIDATE should not be used in patients with pre-existing cardiovascular disorders and should generally not be used in patients with known structural cardiac abnormalities (see CONTRAINDICATIONS; Pre-existing Cardiovascular Disorders and WARNINGS, Cardiovascular).

Children: 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.

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 stimulants or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of 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 judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram 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.

Patients who are considered to need extended treatment with methylphenidate should undergo periodic evaluation of their cardiovascular status (see WARNINGS, Cardiovascular).

Before initiating pms-METHYLPHENIDATE treatment, patients should be assessed for pre-existing and/or family history of psychiatric disorders (see WARNINGS, Cardiovascular). Caution should be exercised in prescribing concomitant drugs.

pms-METHYLPHENIDATE should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

Recommended Dose and Dosage Adjustment

General
Dosage of pms-METHYLPHENIDATE should be individualized according to the needs and responses of the patient.

Dose Titration and Maintenance/Extended Treatment

Children and Adolescents (6 Years and Over)
pms-METHYLPHENIDATE tablets: pms-METHYLPHENIDATE should be initiated in small doses, (e.g., 5-10 mg TID) with weekly increments of 5 to 10 mg in the daily dosage. Dosage should be individualized on the basis of factors such as age, body weight and individual response. Timing of drug administration should be aimed to coincide with periods of greatest academic, behavioural and social stress.

Adults
pms-METHYLPHENIDATE tablets: Administer in divided doses 2 or 3 times daily. Average daily dosage is 20 to 30 mg. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day, should take the last dose before 6 p.m.

Daily dosage above 60 mg is not recommended.

Dose Reduction and Discontinuation

If symptoms do not improve after dose titration over a one month period, the drug should be discontinued.

If symptoms worsen or other adverse events occur, the dosage should be reduced or, if necessary, the drug discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or if necessary, discontinue the drug.

pms-METHYLPHENIDATE should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

Administration

pms-METHYLPHENIDATE is administered orally and can be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Missed Dose
If a dose of Ritalin is missed, patient should take it as soon as possible. The remaining doses for that day should be taken at regularly spaced intervals. The patient should be instructed not take a double dose of RITALIN to make up the missed dose.

Special populations

Renal impairment
No studies have been performed in renally impaired patients.

Hepatic impairment
No studies have been performed in hepatically impaired patients.

Geriatric patients
No studies have been performed in patients over 60 years of age.

PHARMACEUTICAL INFORMATION

Drug Substance

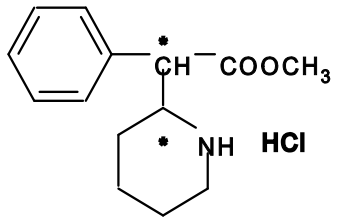
Proper Name: Methylphenidate hydrochloride

Chemical Name: a-phenyl-2-piperidineacetate hydrochloride

Molecular formula: $C_{14}H_{19}NO_2HCl$

Molecular mass: 269.8 g/mol

Structural Formula:



Physicochemical Properties:

Description: White, odorless, fine crystalline powder, solutions which are acid to litmus

Solubility: Freely soluble in water

Composition

pms-METHYLPHENIDATE 5 mg tablets: Each tablet contains medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: Dibasic Calcium Phosphate, FD&C Yellow No. 6, Lactose, Magnesium stearate, Microcrystalline Cellulose and Pregelatinized Starch.

pms-METHYLPHENIDATE 10 mg tablets: Each tablet contains medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: D&C Yellow #10, Dibasic Calcium Phosphate, FD&C Blue #2, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Pregelatinized Starch.

pms-METHYLPHENIDATE 20 mg tablets: Each tablet contains medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: D&C yellow No. 10, Dibasic Calcium Phosphate, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Pregelatinized Starch.

Stability and Storage Recommendations

pms-METHYLPHENIDATE 5 mg, 10 mg, and 20 mg Tablets: Store between 15°C and 30°C.

Keep out of reach and sight of children.

AVAILABILITY OF DOSAGE FORMS

pms-METHYLPHENIDATE tablets 5 mg: Salmon, round, biconvex tablet scored and debossed "MP" over "5" on one side and "130" on the other. Tablets are packaged in bottles of 100 and 500.

pms-METHYLPHENIDATE tablets 10 mg: blue, round, biconvex tablet scored and debossed "MP" over "10" on one side. and "110" on the other. Tablets are packaged in bottles of 100 and 500.

pms-METHYLPHENIDATE tablets 20 mg: Yellow, round, biconvex tablet scored and debossed "MP" over "20" on one side and "123" on the other. Tablets are packaged in bottles of 100 and 500.

TOXICOLOGY

Reproductive Toxicity

Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day. Spina bifida with malrotated hind limb was observed in 2 (out of 18) litters. The no effect level for embryofetal development in rabbits was 60 mg/kg/day (11 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day (4 times the MRHD on a mg/m^2 basis), offspring body weight gain was decreased at the highest dose, but no other effects on postnatal development were observed.

Carcinogenesis-mutagenesis

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 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. 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.

The US Food and Drugs Administration examined data from the Surveillance, Epidemiology and End Results (SEER) database for the years 1973 to 1991 and found that the estimated incidence of hepatoblastoma in the general population was not greater than 1 in 10 million person years.

A total of 174 cases of hepatoblastoma were reported by the SEER for the period 1973 to 1995. Age-adjusted incidence rate was very low (IR = 0, 0382 per 100,000 person years). The majority of cases (149 out of 174) were diagnosed among the age group 0 to 4 years old, which is in accordance with the natural history of the disease. For the age group 5 to 24 years old the rates of hepatoblastoma were very low with few or no cases reported.

On the basis of experience since marketing Methylphenidate Hydrochloride Tablets, there is no evidence that the incidence is higher in patients receiving Methylphenidate Hydrochloride Tablets.

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 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

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 Chinese Hamster Ovary (CHO) cells. In an *in vivo* study of the effect of methylphenidate on bone marrow cells (micronucleus test) there was no evidence of clastogenic or aneugenic effects in mice, at doses up to 250 mg/kg.

Juvenile Neurobehavioral Development

Repeated oral administration of methylphenidate to young rats identified decreased spontaneous locomotor activity at 50 mg/kg/day, due to an exaggerated pharmacological activity of methylphenidate. The systemic exposure in young rats at this dose is 3.4 (male) and 18 (female) times that in children at the maximum recommended human dose (60 mg). In female rats, a deficit in the acquisition of a specific learning task was also observed at the dose of 100 mg/kg/day (the systemic exposure in young female rat at that dose is 28.5 times that in children at the maximum recommended human dose). The clinical relevance of these findings is unknown.

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CONSUMER INFORMATION

pms-METHYLPHENIDATE
Methylphenidate Hydrochloride Tablets, USP
5 mg, 10 mg and 20 mg

This leaflet is part III of a three-part "Product Monograph" published when pms-METHYLPHENIDATE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-METHYLPHENIDATE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

This information for patients or their parents or caregivers is about pms-METHYLPHENIDATE, a medication intended for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) or narcolepsy for adults and children over 6 years of age. It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that pms-METHYLPHENIDATE is only part of the overall management of ADHD. Parents, teachers, healthcare professional's and other professionals are part of a team that must work together.

What the medication is used for:

pms-METHYLPHENIDATE belongs to a group of medicines called central nervous system stimulants. It is used for the treatment of ADHD and narcolepsy. pms-METHYLPHENIDATE tablets contain methylphenidate hydrochloride, the active ingredient in the treatment of ADHD and narcolepsy.

1) When used in ADHD, pms-METHYLPHENIDATE improves behaviour by reducing restlessness and increasing attention. pms-METHYLPHENIDATE, however, will not cure ADHD. Treatment with pms-METHYLPHENIDATE or other stimulants should always be combined with other treatment measures, such as psychological counseling and educational tutoring by skilled and experienced therapists.

Children and/or adolescents treated with pms-METHYLPHENIDATE do not seem to become addicted or abuse drugs later in life. However, central nervous stimulants, including pms-METHYLPHENIDATE, should only be given under close medical supervision to patients whose condition has been properly diagnosed.

About ADHD
ADHD is a disorder characterized by symptoms of inattentiveness and/or hyperactivity-impulsivity inappropriate to the patient's age, which interfere with functioning in two or more settings (e.g., school and home). Symptoms of inattention may include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity-impulsiveness may include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have both types of symptoms. Symptoms must be present for at least 6 months to be certain of the diagnosis.

2) When used in narcolepsy, pms-METHYLPHENIDATE may relieve the inappropriate daytime sleepiness; however, many people suffering from narcolepsy need additional treatment aimed at other aspects of this condition.

About Narcolepsy
Persons who suffer from narcolepsy experience attacks of sleepiness during the day although they may have enough sleep at night. These attacks usually occur in unusual situations such as standing, eating or the middle of a conversation. Some people find their head falling forward, jaw dropping, knees buckling or even falling to the ground while they are conscious. These attacks may be brought on by emotional situations such as hearty laughter, excitement, sadness or anger.

What it does:

ADHD
pms-METHYLPHENIDATE works by improving the activity of certain parts of the brain which are underactive. pms-METHYLPHENIDATE improves attention (attention span) and concentration, and reduces impulsive behaviour.

Narcolepsy
pms-METHYLPHENIDATE relieves excessive daytime sleepiness in patients suffering from narcolepsy.

When it should not be used:
pms-METHYLPHENIDATE should not be used if you or your child:

- Have 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.
- Have moderate to severe high blood pressure (hypertension) or narrowing of the blood vessels (arterial occlusive disease that can cause pain in the arms and legs).
- Have arteriosclerosis (hardened arteries)
- Have any thyroid problems
- Have significant anxiety, tension, or agitation since pms-METHYLPHENIDATE may make these conditions worse.
- Are allergic to methylphenidate or any of the other ingredients in pms-METHYLPHENIDATE (see What the non-medicinal ingredients are). If you think you may be allergic, talk to your doctor for advice.
- Have increased eye pressure (glaucoma).
- Have Tourette's syndrome, including uncontrolled speech (verbal tics) and body movements (motion tics) or a family history of Tourette's syndrome.
- Are taking a medicine called a monoamine oxidase inhibitor (MAOI) used for depression, or have taken an MAOI in the last 14 days (see Interactions with this medication).
- Have a tumor of the adrenal gland called pheochromocytoma.

What the medicinal ingredient is:
Methylphenidate hydrochloride

What the non-medicinal ingredients are:
5 mg: Dibasic Calcium Phosphate, FD&C Yellow No. 6, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Pregelatinized Starch.

10 mg: D&C Yellow #10, Dibasic Calcium Phosphate, FD&C Blue #2, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Pregelatinized Starch.

20 mg: D&C Yellow No. 10, Dibasic Calcium Phosphate, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Pregelatinized Starch.

What dosage forms it comes in:

pms-METHYLPHENIDATE 5 mg, tablets are packaged in bottles of 100 and 500.
pms-METHYLPHENIDATE 10 mg tablets are packaged in bottles of 100 and 500.
pms-METHYLPHENIDATE 20 mg tablets are packaged in bottles of 100 and 500.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drug Abuse and Dependence
Abuse of pms-METHYLPHENIDATE can lead to dependence. Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

The following have been reported with use of pms-METHYLPHENIDATE and other medicines used to treat ADHD:

1. Heart-related Problems:
- **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, pms-METHYLPHENIDATE generally should not be used in children, adolescents or adults with known structural heart abnormalities or other serious heart disease or conditions.

Tell your doctor if you or, your child, have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor may wish to check you or your child carefully for heart problems before starting pms-METHYLPHENIDATE.

Your doctor may wish to check your or your child's blood pressure and heart rate regularly during treatment with pms-METHYLPHENIDATE.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking pms-METHYLPHENIDATE.

2. Mental (Psychiatric) Problems:

- **new or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (including suicide attempt, suicidal ideation and completed suicide)**
- **new or worse bipolar illness, characterized by extreme mood swings, with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness)**
- **new or worse aggressive behaviour or hostility**
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

These new or worse mental problems may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your doctor about any mental problems or about any personal or family history of suicide, bipolar illness, or depression you or your child have.

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 pms-METHYLPHENIDATE. **Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation.**

Call your doctor right away if you or your child has any new or worsening mental symptoms or problems while taking pms-METHYLPHENIDATE, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

Tell your doctor immediately if you experience abnormally sustained or frequent and painful erections of the penis on pms-METHYLPHENIDATE treatment or after treatment discontinuation. This can occur in any age group and may need urgent medical treatment.

Serotonin toxicity (also known as Serotonin syndrome): pms-METHYLPHENIDATE can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take pms-METHYLPHENIDATE 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

BEFORE you or your child use pms-METHYLPHENIDATE talk to your doctor or pharmacist if you or your child:

- Have structural heart abnormalities.
- Have a family history of sudden death or death related to heart problems.
- Have any other current or previous heart problems
- Do strenuous exercise.
- Take other stimulant drugs.
- Have a history of drug or alcohol abuse.
- Have motion tics or if any other family members suffer from tics. Signs of tics that are hard to control, repeated twitching of any parts of the body or repeating sounds and words.
- Have someone in your family with Tourette's syndrome.
- Have had fits (convulsions, epilepsy, seizures) or abnormal EEGs (electroencephalograms).
- Have mild high blood pressure.
- Have an abnormal heart rate or rhythm.
- Have or have had any disorder of the blood vessels in the brain, e.g., weakening of blood vessels (aneurysm), stroke, inflammation of blood vessels (vasculitis).
- Have aggressive behaviour.
- Have any suicidal thoughts or behaviour.
- Have mental problems or family history of mental problems, including psychosis, mania, bipolar illness, depression or suicide.
- Have circulation problems in fingers and toes, including numbness; feeling cold or pain. (This is also known as Raynaud's).
- Are over 60 years of age.
- Are lactose intolerant or have one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency, Glucose-galactose malabsorption. Because lactose is a non-medicinal ingredient in pms-METHYLPHENIDATE.

Tell your doctor immediately if you develop any of the above conditions or symptoms while taking pms-METHYLPHENIDATE. The doctor will decide if you can start or continue taking pms-METHYLPHENIDATE.

Before taking pms-METHYLPHENIDATE, tell your doctor if you are pregnant or plan for pregnancy (women and men).

If you take pms-METHYLPHENIDATE, it can be in your breast milk. Do not breast-feed during your treatment with pms-METHYLPHENIDATE. Tell your doctor if you are nursing a baby.

pms-METHYLPHENIDATE may cause dizziness, drowsiness, blurred vision, hallucination or other central nervous system side effects, which can affect concentration. If you experience such symptoms, do not drive or use machines, or do other activities that need quick reactions until you know how this medication affects you.

Monitoring during treatment with pms-METHYLPHENIDATE
To see if pms-METHYLPHENIDATE is having any unwanted effects, the doctor will check from time to time the patient's health conditions (e.g., blood pressure, heart rate) and will also monitor the growth of children taking pms-METHYLPHENIDATE. Blood tests will be carried out to monitor the amount of blood cells (white blood cells, red blood cells and platelets) if a patient takes pms-METHYLPHENIDATE for a long time.
pms-METHYLPHENIDATE should not be used in children under 6 years of age.

INTERACTIONS WITH THIS MEDICATION

Both your doctor and your pharmacist should also be informed of all medicines you are taking, including herbal medicines or drugs are not taken on a regular basis and are available without prescription.

Do not take pms-METHYLPHENIDATE if you are taking
- A medicine called a monoamine oxidase inhibitor (MAOI, used to treat depression), or have taken an MAOI in the last 14 days. Taking a MAOI with pms-METHYLPHENIDATE may cause a sudden increase in your blood pressure (see When it should not be used).

pms-METHYLPHENIDATE may change the way your body reacts to certain medicines. It is important that you tell your doctor or pharmacist if you are taking any of these medicines, it may be necessary to change the dose or in some cases to stop one of the medicines. These include:

- medicines that increase blood pressure,
- phenylbutazone (used to treat pain or fever),
- alpha-2 agonists like clonidine (used to treat high blood pressure),
- medicines used to treat depression,
- medicines used to prevent seizures,
- medicines used to prevent blood clots, e.g., coumarin anticoagulants (commonly called "blood thinners"),
- medicines that influence the level of dopamine in the body (dopaminergic medicines used to treat Parkinson's disease or psychosis),
- medicines that raise the level of serotonin in the body (serotonergic medicines, for example those used to treat depression like sertraline and venlafaxine).

Having an Operation
If you are going to have an operation, tell the doctor that you are on treatment with pms-METHYLPHENIDATE. You should not take pms-METHYLPHENIDATE on the day of your operation if a certain type of anesthetic is used. This is because there is a chance of a sudden rise in blood pressure and heartbeat during the operation.

Taking pms-METHYLPHENIDATE with Food and Drink
Do not drink alcohol while taking pms-METHYLPHENIDATE. Alcohol may make the side effects of pms-METHYLPHENIDATE worse. Remember that some foods and medicines contain alcohol.

Drug Testing
pms-METHYLPHENIDATE may give a false positive result when testing for drug use. This includes testing used in sport.

PROPER USE OF THIS MEDICATION

Usual dose:
pms-METHYLPHENIDATE comes in tablets to be taken by mouth. The doctor determines how much and how often you should take pms-METHYLPHENIDATE according your individual needs. In order for you to receive the most benefits from pms-METHYLPHENIDATE, it is important that pms-METHYLPHENIDATE be taken only as directed by the doctor. Take only the amount of medication at the time intervals and for the time period that the doctor has prescribed.

Children should not take more than 60 mg of pms-METHYLPHENIDATE per day.

Overdose

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

The symptoms of overdose are vomiting, agitation, headache, tremors, muscle twitching, irregular heartbeat, flushing, fever, sweating, dilated pupils, breathing difficulties, confusion, and fits; muscle spasms, fever, red-brown coloured urine which could be possible signs of abnormal breakdown of muscles (rhabdomyolysis).

Missed Dose
If a dose of pms-METHYLPHENIDATE is missed, you should take it as soon as possible. The remaining doses for that day should be taken at regularly spaced intervals. Do not take a double dose of pms-METHYLPHENIDATE to make up the missed dose. If you have any questions about this, check with the doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, pms-METHYLPHENIDATE can have some side effects, although not everybody gets them. These are usually mild to moderate and generally do not last long.

Taking pms-METHYLPHENIDATE with food may reduce stomach discomfort.

pms-METHYLPHENIDATE may cause sleeplessness if taken too close to bedtime.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your pms-METHYLPHENIDATE treatment.

Some side effects are very common:
These side effects may affect more than 1 in 10 patients.

- sore throat and runny nose
- decreased appetite
- nervousness
- difficulty in falling asleep
- nausea, dry mouth

Some side effects are common:
These side effects may affect between 1 and 10 in every 100 patients.

- excessive emotional distress, troubled, sleep disturbance, emotional excitement, restlessness
- trembling, headache, dizziness, sleepiness
- changes in blood pressure (usually an increase), abnormal heart rhythm, palpitation
- cough
- vomiting, stomach pain, upset stomach, indigestion, toothache
- skin rash, itchy rash and hives (urticaria), fever, hair loss
- excessive sweating
- joint pain
- decreased weight
- feeling jittery
- feeling depressed (depression)
- feeling aggressive (aggression)
- excessive teeth grinding (bruxism)

Some side effects are uncommon:
These side effects may affect between 1 and 10 in every 1,000 patients.

- spasm of the jaw muscles that makes it difficult to open the mouth (trismus)

Some side effects are rare:
These side effects may affect between 1 and 10 in every 10,000 patients.

- slowing of growth (height and weight) during prolonged use in children
- trouble seeing

Some side effects are very rare:
These side effects may affect less than 1 in every 10,000 patients.

- low red blood cell count (anemia), low platelet count (thrombocytopenia)
- unusually active, depressed mood
- uncontrolled speech and body movements (Tourette's syndrome)
- abnormal liver function including liver coma
- muscle cramps

Some other side effects (Frequency: Not Known):

- irritated, mood changes, abnormal behaviour or thinking, anger, excessive awareness of surroundings, feeling disorientated, changes in sex drive, lack of feeling or emotion, doing things over and over again, being obsessed with one thing, confusion, addiction
- temporary muscle weakness, loss of skin sensation or other functions of the body due to a temporary lack of blood supply to the brain (reversible ischaemic neurological deficit), migraine
- double vision, dilated pupils
- stopped heartbeat, heart attack
- shortness of breath
- diarrhea, constipation
- swelling of face and throat, redness of the skin, large red blotches on the skin appearing within a few hours of taking the medicine
- muscle pain
- blood in the urine
- swelling of the breasts in men
- tiredness
- abnormal sounds from heart
- stuttering (dysphemia)
- bedwetting in children during the night (enuresis)

Other side effects not listed above may occur in some patients. If you notice any other effects, tell your doctor immediately.

This is not a complete list of possible side effects. Ask your doctor about other side effects. If any side effects develop, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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	**Heart problems:** Fast or uneven heartbeat, chest pain, difficulty breathing, fainting			✓
	Dyskinesia: uncontrollable twitching and jerking			✓
	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			✓
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			✓
	Neuroleptic Malignant Syndrome: sudden high fever, very high blood pressure and severe			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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**	
	convulsions			
	Thrombocyto-penic purpura: bleeding under the skin, bruising		✓	
	Muscle twitching or tics	✓		
	Low white blood cell count: sore throat and fever or chills	✓		
	Choreoathetoid movements: uncontrollable writhing movements of the limb, face and/or trunk		✓	
	Hallucinations: seeing or feeling things that are not really there			✓
	Seizures: (fits): uncontrollable shaking with or without loss of consciousness			✓
	Exfoliative dermatitis: skin blisters or itching			✓
	Erythema multiforme: red blotches on the skin		✓	
Rare	**Blurred vision**		✓	
Unknown	**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)		✓	
	Aggressive Behaviour or		✓	
	Hostility			
	Suicidal Behaviour: Thoughts or actions about hurting or killing yourself (including completed suicide)			✓
	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	✓		

This is not a complete list of side effects. For any unexpected effects while taking pms-METHYLPHENIDATE, contact your doctor or pharmacist.

HOW TO STORE IT

Store pms-METHYLPHENIDATE tablets between 15°C and 30°C.

pms-METHYLPHENIDATE should not be used after the expiry date shown on the package label. Remember to take back unused medicine to your pharmacist.

Keep pms-METHYLPHENIDATE out of reach and sight of children.

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.

MORE INFORMATION

If you want more information about pms-METHYLPHENIDATE:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

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