Product Monograph

Including Patient Medication Information

AA-METHYLPHENIDATE SR

Methylphenidate Hydrochloride Extended-Release Tablets

For Oral use

20 mg of Methylphenidate hydrochloride

USP

Central Nervous System Stimulant

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Recent Major Label Changes

None at time of the most recent authorization

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

AA-METHYLPHENIDATE SR (methylphenidate hydrochloride extended-release tablets) is indicated for the treatment of:

- Narcolepsy
- Attention Deficit Hyperactivity Disorder (ADHD)

Need for Comprehensive Treatment Program
AA-METHYLPHENIDATE SR 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 extended-release tablets for long-term use in ADHD, i.e. for more than 4 weeks has not been systematically evaluated in placebo-controlled trials. Therefore, the healthcare professional who elects to use AA-METHYLPHENIDATE SR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.1. Pediatrics

Pediatrics (<6 years of age): AA-METHYLPHENIDATE SR should not be used in children under 6 years of age. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients under 6 years of age. See 7.1.3. Pediatrics.

Pediatrics (6 to 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AA-METHYLPHENIDATE SR in pediatric patients aged 6 years to 18 years has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 4.2. Recommended Dose and Dosage Adjustment.

1.2. 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. See 7.1.4. Geriatrics.

2. Contraindications

AA-METHYLPHENIDATE SR is contraindicated in the following conditions:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging.
- 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 7. Warnings and Precautions, Cardiovascular.
- Glaucoma.
- Pheochromocytoma.
- Patients with motor tics and/or family history or diagnosis of Tourette's syndrome. See 7. Warnings and Precautions, Neurologic.
- 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 9.1. Serious Drug Interactions.

3. Serious Warnings and Precautions Box

Drug Dependence - Like other stimulants, AA-METHYLPHENIDATE SR has the potential to be abused, leading to dependence and tolerance. See 7. Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability.

4. Dosage and Administration

4.1. Dosing Considerations

AA-METHYLPHENIDATE SR (methylphenidate hydrochloride extended-release tablets) 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.

AA-METHYLPHENIDATE SR 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 2. Contraindications, Pre-existing cardiovascular disorders and 7. Warnings and Precautions, 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 7. Warnings and Precautions, Cardiovascular.

Before initiating AA-METHYLPHENIDATE SR treatment, patients should be assessed for pre-existing and/or family history of psychiatric disorders. See 7. Warnings and Precautions, Neurologic.

Caution should be exercised in prescribing concomitant drugs.

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

4.2. Recommended Dose and Dosage Adjustment

General

Dosage of AA-METHYLPHENIDATE SR (methylphenidate hydrochloride extended-release tablets) should be individualized according to the needs and responses of the patient.

Dose Titration and Maintenance/Extended Treatment

AA-METHYLPHENIDATE SR extended-release tablets have a duration of action of approximately 8 hours. Therefore, AA-METHYLPHENIDATE SR tablets may be used in place of methylphenidate hydrochloride tablets when the 8-hour dosage of AA-METHYLPHENIDATE SR corresponds to the titrated 8-hour dosage of methylphenidate hydrochloride

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.

AA-METHYLPHENIDATE SR 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.

4.4. Administration

AA-METHYLPHENIDATE SR tablets are administered orally and can be taken with or without food (see 10.3. Pharmacokinetics). AA-METHYLPHENIDATE SR tablets must be swallowed whole and never be crushed or chewed.

4.5. Missed Dose

If a dose of AA-METHYLPHENIDATE SR is missed, the 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 AA-METHYLPHENIDATE SR to make up the missed dose.

5. Overdose

Signs and symptoms of acute overdose, 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.

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 over dosage has not been established.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Extended-release tablet / 20 mg	Colloidal silicon dioxide, hydroxypropyl methylcellulose and magnesium stearate

Description

Each round, white to off-white, biconvex tablet, engraved "APO" on one side, "SR" over "20" on the other side contains 20 mg methylphenidate hydrochloride. Available in bottles of 100.

AA-METHYLPHENIDATE SR is a controlled drug.

7. Warnings and Precautions

See 3. Serious Warnings and Precautions Box.

General

Fatigue

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

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, AA-METHYLPHENIDATE SR 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 2. 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 judgement, 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 methylphenidate hydrochloride, may be associated with sudden death and other serious cardiovascular adverse events. See 7. Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability

Hypertension and other Cardiovascular Conditions

AA-METHYLPHENIDATE SR 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 2. Contraindications, Pre-existing cardiovascular disorders.

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants used to treat ADHD, such as methylphenidate hydrochloride, 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 and/or Abuse Liability

AA-METHYLPHENIDATE SR contains methylphenidate, a Schedule III Controlled Substance. Like other stimulants, AA-METHYLPHENIDATE SR has the potential for abuse and long-term use can lead to the development of tolerance. AA-METHYLPHENIDATE SR 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 3. Serious Warnings and Precautions Box and 7. Warnings and Precautions Misuse and Cardiovascular Events.

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 during childhood and/or adolescence does not seem to result in increased predisposition for addiction.

Driving and Operating Machinery

AA-METHYLPHENIDATE SR may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects. See 8.2. Clinical Trial Adverse Reactions. Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

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, in children. See 8.2. Clinical Trial Adverse Reactions. Growth should be monitored as clinically necessary during treatment with AA-METHYLPHENIDATE SR, 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.

Hematologic

Long-term effects of methylphenidate hydrochloride 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 8.2. Clinical Trial Adverse Reactions.

Neurologic

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 AA-METHYLPHENIDATE SR. 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 AA-METHYLPHENIDATE SR. See7. Warnings and Precautions, Cardiovascular and 9.1. Serious Drug Interactions.

Seizures
There is some clinical evidence that methylphenidate hydrochloride 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. 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 9.4. Drug-Drug Interactions. Other common serotonergic drugs include: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) (see 2. Contraindications), serotonin 5-HT_1 receptor agonists (triptans), and 5-HT_3 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 methylphenidate hydrochloride 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). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Tics
Methylphenidate hydrochloride is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. See 8.2. Clinical Trial 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. AA-METHYLPHENIDATE SR is contraindicated in case of diagnosis or family history of Tourette's syndrome (see 2. Contraindications). Patients should be regularly monitored for the emergence or worsening of tics during treatment with AA-METHYLPHENIDATE SR.

Ophthalmologic

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

Psychiatric

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with AA-METHYLPHENIDATE SR, patients should be assessed for pre-existing and/or a family history of psychiatric disorders. See 4.1. Dosing Considerations.

Treatment of ADHD with stimulant products including AA-METHYLPHENIDATE SR 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.

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

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 professionals 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 8.5. Post-Market Adverse Reactions.

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

Reproductive Health

- **Function:**

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

7.1. Special Populations

7.1.1. Pregnancy

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

7.1.2. Breastfeeding

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5. See 10.3. Pharmacokinetics, Special populations and conditions, Pregnancy and breastfeeding.

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

7.1.3. Pediatrics

Pediatrics (<6 years of age): AA-METHYLPHENIDATE SR should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

Pediatrics (6 to 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AA-METHYLPHENIDATE SR in pediatric patients aged 6 years to 18 years has been established.

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 AA-METHYLPHENIDATE SR (methylphenidate hydrochloride extended-release tablets) 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 methylphenidate hydrochlorideis usually not indicated.

7.1.4. 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.

8. Adverse Reactions

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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 methylphenidate hydrochloride 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 lymphatic system disorders

Very rare: leukopenia, thrombocytopenia, anemia.

Cardiac disorders

Common: palpitations, tachycardia, cardiac arrhythmia.

Rare: angina pectoris.

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, fever.

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: blood pressure increased, heart rate increased, 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.

Metabolism and nutrition disorders

Very common: decreased appetite.

Rare: slight growth retardation during prolonged use in children, moderately reduced weight gain during prolonged use in children.

Musculoskeletal and connective tissue disorders

Common: arthralgia.

Very rare: muscle cramps.

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, cerebral hemorrhages and cerebrovascular accidents.

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 played in these cases.

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, alopecia, hyperhidrosis.

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

Vascular disorders

Very rare: vasculitis.

8.5. Post-Market Adverse Reactions

Blood and 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 7. Warnings and Precautions, Psychiatric.

Renal and urinary disorders: Enuresis

Reproductive system and breast disorders: Priapism: Priapism has been reported with methylphenidate products, including methylphenidate hydrochloride. See 7. Warnings and Precautions, Reproductive Health.

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 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 skin rash, urticaria, fever, epistaxis, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, thrombocytopenic purpura, angioedema and anaphylactic reaction, photosensitivity reaction, skin discolouration, skin odor abnormal, anorexia, muscle cramps, trismus, convulsions, choreoathetoid movements, dyskinesia, malaise, nausea, abdominal pain, weight loss during prolonged therapy, rebound effect, akathisia, presyncope, somnambulism, speech disorder, syncope, dysphemia, euphoric mood, visual impairment, visual disturbance, difficulties in accommodation, ear disorder, dizziness, incontinence, drowsiness, headache, pulse changes, peripheral vascular disease, vasodilation, cardiac arrythmias, tachycardia, angina, ECG QT prolongation, anger, change in sustained attention, crying, depersonalization, dermatilomania, hallucination (sometimes visual, auditory and/or tactile), impulsive behaviour, logorrhea, obsessive-compulsive disorder, neurosis, onychophagia, oppositional defiant disorder, accidental injury, anemia, aplastic anemia and pancytopenia, leucopenia, thrombocytopenia, and hypoglycemia. There have been rare reports of Tourette's syndrome and rhabdomyolysis. 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 and connective tissue disorders: Myalgia, muscle twitching.

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.

9. Drug Interactions

9.1. Serious Drug Interactions

- **Monoamine Oxidase inhibitors:** Because of possible hypertensive crisis, AA-METHYLPHENIDATE SR is contraindicated in patients being treated (currently or within the preceding 14 days) with MAO-inhibitors. See 2. Contraindications.
  Use AA-METHYLPHENIDATE SR with caution in patients being treated with drugs that elevate blood pressure. See 7. Warnings and precautions, Neurologic.
- **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.

9.2. Drug Interactions Overview

Methylphenidate hydrochloride is 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 pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate in methylphenidate hydrochloride did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

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

9.3. Drug-Behaviour Interactions

Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including AA-METHYLPHENIDATE SR. Patients should be advised to abstain from alcohol during treatment.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 2 – Established or Potential Drug-Drug Interactions

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Anesthetics	T	With halogenated anesthetics, there is a risk of sudden blood pressure and heart rate increase during surgery. AA-METHYLPHENIDATE SR may also antagonize the sedative effect of general anesthetics.	If surgery is planned, AA-METHYLPHENIDATE SR should not be taken on the day of surgery.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Anti-hypertensive drugs	T	AA-METHYLPHENIDATE SR may decrease the effectiveness of drugs used to treat hypertension.	
Coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, diphenylhydantoin, primidone), phenylbutazone and tricyclic antidepressants	T	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. An interaction with the anticoagulant ethylbiscoumacetate in 4 subjects was not confirmed in a subsequent study with a larger sample size (n=12).	Downward dosage adjustments of these drugs might be required when given concomitantly with AA-METHYLPHENIDATE SR.
Dopaminergic drugs	T	As an inhibitor of dopamine reuptake, methylphenidate hydrochloride may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA (3,4-dihydroxphenylalanine) and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g. haloperidol).	Concomitant use of AA-METHYLPHENIDATE SR 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 AA-METHYLPHENIDATE SR with antipsychotics may increase the risk of EPS when there is a change (increase or decrease) in dosage of either or both medications.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Serotonergic drugs	T	Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.	The concomitant use of AA-METHYLPHENIDATE SR and serotonergic drugs is not recommended as this may lead to the development of serotonin toxicity. See 7. Warnings and Precautions, Neurologic.

Legend: T = Theoretical

Other specific drug-drug interaction studies with methylphenidate hydrochloride have not been performed *in vivo*.

9.5. Drug-Food Interactions

Administration of methylphenidate hydrochloride with food accelerated absorption, but had no effect on the amount absorbed. See 10.3 Pharmacokinetics.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

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

10. Clinical Pharmacology

10.1. Mechanism of Action

AA-METHYLPHENIDATE SR is a 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).

10.2. Pharmacodynamics

Methylphenidate hydrochloride is a racemate consisting of a 1:1 mixture of d-methylphenidate (d-MPH) and l-methylphenidate (l-MPH).

10.3. 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 to 52%). In one study, the administration of methylphenidate hydrochloride with food accelerated absorption, but had no effect on the amount absorbed.

Methylphenidate in the extended-release tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the methylphenidate hydrochloride extended-release tablet, compared to the methylphenidate hydrochloride tablet, measured by the urinary excretion of the methylphenidate major metabolite (a-phenyl-2-piperidine acetic acid, PPAA), was 105% (49 to 168%) in children and 101% (85% to 152%) in adults. The time to peak rate in children was 4.7 hours (1.3 to 8.2 hours) for the extended-release tablets and 1.9 hours (0.3 to 4.4 hours) for the regular tablets.

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 (C_{max}) showed dose-proportionality.

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%).

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 to 33 L/kg). The volume of distribution after an intravenous dose (V_{ss}) is 2.23 L/kg for the racemate in healthy adult volunteers.

Following oral administration of methylphenidate, 78 to 97% of the dose is excreted in the urine and 1 to 3% in the feces in the form of metabolites within 48 to 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.

The elimination half-life and the cumulative urinary excretion of PPAA are not significantly different between the two dosage forms. An average of 67% of the extended-release tablet dose was excreted in children as compared to 86% in adults.

Special populations and conditions

- **Pediatrics:** Methylphenidate hydrochloride should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established. See 7.1.3. Pediatrics.
- **Geriatrics:** No studies have been performed in patients over 60 years of age. See 7.1.4. Geriatrics.

- **Pregnancy and breastfeeding:** AA-METHYLPHENIDATE SR should not be given to pregnant women unless the potential benefit outweighs the risk to fetus. See 7.1.1. Pregnancy.

  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. See 7.1.2. Breastfeeding.

- **Hepatic Insufficiency:** No studies have been performed in patients with hepatic impairment.
- **Renal Insufficiency:** No studies have been performed in patients with renal impairment.

11. Storage, Stability and Disposal

Protect from heat and humidity. Store between 15°C-30°C.

Keep out of reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

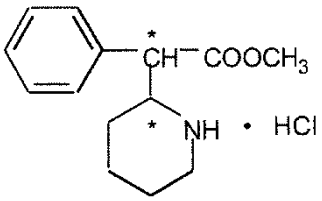
Non-proprietary name of the drug substance: Methylphenidate hydrochloride

Chemical name:

1) 2-Piperidineacetic acid, ∀-phenyl-, methyl ester, hydrochloride, (R*,R*)-(∀)-
2) Methyl ∀-phenyl-2-piperidineacetate hydrochloride

Molecular formula and molecular mass: $C_{14}H_{19}NO_2HCl$ and 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

14. Clinical Trials

14.1 Clinical trial by indication

No clinical trial data is available for AA-METHYLPHENIDATE.

14.2. Comparative Bioavailability Studies

AA-METHYLPHENIDATE SR 20 mg tablets: Comparative bioavailability studies were performed using healthy adult volunteers. The rate and extent of absorption of methylphenidate were measured and compared following administration of a 20 mg dose of either AA-METHYLPHENIDATE SR 20 mg tablets or RITALIN® SR 20 mg tablets under fasting and fed conditions. The results from measured data are summarized in Table 3 and Table 4.

Table 3 - Summary Table of the Comparative Bioavailability Data Under Fasting Conditions

Methylphenidate HCL Extended Release (A single 20 mg dose: 1 x 20 mg) From measured data Under Fasting Conditions - Based on Methylphenidate Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test AA-METHYLPHENIDATE SR**	**Reference RITALIN®SR†**	**% Ratio of Geometric Means****	**90% Confidence Interval**
AUC_T (pg -hr/mL)	37369 39532 (34)	37064 39115 (34)	100.8	(95.6 - 106.3)
AUC_I (pg -hr/mL)	39007 41000 (33)	38523 40503 (34)	101.3	(96.8 - 105.9)
C_{max} (pg /mL)	4643 4848 (31)	4956 5185 (32)	93.7	(87.3 - 100.6)
T_{max}^{*} (h)	4.86 (12)	4.47 (21)		
$T_{½}^{*}$ (h)	4.14 (17)	3.37 (22)		

* Expressed as the arithmetic mean (CV%)

** Based on the least square means.

† RITALIN® SR is marketed by Novartis Pharmaceuticals Canada Inc. (Dorval, QC, Canada), and was purchased in Canada.

Table 4 - Summary Table of the Comparative Bioavailability Data Under Fed Conditions

Methylphenidate HCL Extended Release (A single 20 mg dose: 1 x 20 mg) From measured data Under Fed Conditions - Based on Methylphenidate Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test AA-METHYLPHENIDATE SR**	**Reference RITALIN®SR†**	**% Ratio of Geometric Means****	**90% Confidence Interval**
AUC_T (pg -hr/mL)	54979 62430 (74)	54486 61267 (68)	100.9	(98.1 - 103.8)
AUC_I (pg -hr/mL)	56664 65167 (79)	55944 63221 (70)	101.3	(98.4 - 104.2)
C_{max} (pg /mL)	7027 7692 (60)	7157 7946 (64)	98.2	(92.6 - 104.1)
T_{max}^{*} (h)	3.72 (33)	3.70 (28)		
$T_{½}^{*}$ (h)	4.19 (22)	3.45 (24)		

* Expressed as the arithmetic mean (CV%)

** Based on the least square means.

† RITALIN® SR is marketed by Novartis Pharmaceuticals Canada Inc. (Dorval, QC, Canada), and was purchased in Canada.

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 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.

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 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, there is no evidence that the incidence is higher in patients receiving methylphenidate hydrochloride.

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.

Reproductive and developmental toxicology

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.

Juvenile toxicity

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.

17. Supporting Product Monographs

1) RITALIN® SR (methylphenidate hydrochloride extended-release tablets, 20 mg), control number 260742, product monograph, Novartis Pharmaceuticals Canada Inc. (2022-06-22)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AA-METHYLPHENIDATE SR

Methylphenidate Hydrochloride Extended-Release Tablets

This Patient Medication Information is written for the person who will be taking **AA-METHYLPHENIDATE SR**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **AA-METHYLPHENIDATE SR**, talk to a healthcare professional.

Serious warnings and precautions box

Drug Dependence:

Like other stimulants, AA-METHYLPHENIDATE SR has the potential to be abused. This can lead to you becoming dependent on AA-METHYLPHENIDATE SR, or feeling like you need to take more of it over time. Talk to a healthcare professional if you have an interest in drugs or alcohol, or have a history of drug or alcohol abuse.

What AA-METHYLPHENIDATE SR is used for:

AA-METHYLPHENIDATE SR is used in children 6 years of age or older, adolescents and adults for the treatment of:

- attention-deficit hyperactivity disorder (ADHD) and
- narcolepsy.

How AA-METHYLPHENIDATE SR works:

AA-METHYLPHENIDATE SR belongs to a group of medicines called central nervous system stimulants. It works by changing the levels of certain chemicals in the brain. In patients with ADHD, AA-METHYLPHENIDATE SR helps to improve attention (attention span) and decrease impulsivity and hyperactivity. In patients with narcolepsy, AA-METHYLPHENIDATE SR relieves excessive daytime sleepiness.

The ingredients in AA-METHYLPHENIDATE SR are:

Medicinal ingredient: Methylphenidate hydrochloride

Non-medicinal ingredients: Colloidal silicon dioxide, hydroxypropyl methylcellulose and magnesium stearate.

AA-METHYLPHENIDATE SR comes in the following dosage forms:

Extended-Release Tablets: 20 mg.

Do not use AA-METHYLPHENIDATE SR if:

- you are allergic to methylphenidate hydrochloride or to any of the other ingredients in AA-METHYLPHENIDATE SR.
- you 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.
- you 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).
- you have a condition called arteriosclerosis (hardened arteries)
- you have any thyroid problems
- you have significant anxiety, tension, or agitation since AA-METHYLPHENIDATE SR may make these conditions worse.
- you have glaucoma (an eye disease that causes increased eye pressure).
- you have Tourette's syndrome, including uncontrolled speech (verbal tics) and body movements (motion tics) or a family history of Tourette's syndrome.
- you are taking or have taken in the past 14 days, a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI) .
- you have a condition called pheochromocytoma (a rare tumor that usually grows in the adrenal glands, above your kidneys).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AA-METHYLPHENIDATE SR. Talk about any health conditions or problems you may have, including if you or your child:

- have structural heart abnormalities.
- have a family history of sudden death or death related to heart problems.
- do strenuous exercise.
- take other stimulant drugs.
- have a history of drug or alcohol abuse
- have a history of fits (convulsions, epilepsy, seizures) or abnormal EEGs (electroencephalograms – measure of brainwave activity).
- have mild high blood pressure.
- 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 mental health problems or a family history of mental health problems, including:
    - anxiety,
    - psychosis,
    - mania,
    - bipolar illness,
    - depression,
    - aggression,
    - suicide.
- have a disorder that affects the blood vessels outside your heart and brain. This includes a condition called Raynaud's phenomenon, which causes circulation problems in your fingers and toes, including

numbness, feeling cold or pain.
- are over 60 years of age.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. AA-METHYLPHENIDATE SR can pass into your breast milk. Do not breastfeed during your treatment with AA-METHYLPHENIDATE SR. Tell your healthcare professional if you are nursing a baby.

Other warnings you should know about:

Dependence and tolerance: Like other stimulants, AA-METHYLPHENIDATE SR has the potential to be abused, leading to dependence and tolerance. If you have a history of drug or alcohol abuse, talk to your healthcare professional. Do not change your dose or stop taking AA-METHYLPHENIDATE SR without first talking to your healthcare professional. If you stop taking AA-METHYLPHENIDATE SR, you will need careful supervision because you may feel very depressed.

Driving and using machines: AA-METHYLPHENIDATE SR can affect your ability to drive and use tools or machinery. You should not drive or use tools or machinery until you know how you respond to AA-METHYLPHENIDATE SR.

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

Heart-related problems: The following heart related problems have been reported in people taking medication to treat ADHD, like AA-METHYLPHENIDATE SR:
- 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 in association with stimulant drugs for ADHD treatment in children with structural heart abnormalities. AA-METHYLPHENIDATE SR generally should not be used in children, adolescents or adults with known structural heart abnormalities.

Tell your healthcare professional if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems. Your healthcare professional will check:
- you for heart problems before starting AA-METHYLPHENIDATE SR
- your blood pressure and heart rate regularly during treatment with AA-METHYLPHENIDATE SR

Seek immediate medical help if you have any signs of heart problems such as chest pain, shortness of breath, or fainting while taking AA-METHYLPHENIDATE SR.

Mental health problems: The following mental health problems have been reported in people taking medicine to treat ADHD like AA-METHYLPHENIDATE SR:
- new or 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 symptoms of bipolar disorder (extreme mood swings, with periods of impulsiveness or unusual excitement, switching between periods of sadness)

- new or worse aggressive behaviour or hostility
- new psychotic symptoms (such as hearing voices, believing things that are not true, being suspicious)

These new or worse mental symptoms may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your healthcare professional about any mental problems 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 AA-METHYLPHENIDATE SR.

Seek immediate medical help if you have any mental health symptoms while taking AA-METHYLPHENIDATE SR.

Serotonin toxicity (also known as Serotonin Syndrome): AA-METHYLPHENIDATE SR may cause serotonin syndrome, 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 AA-METHYLPHENIDATE SR with other serotonergic drugs such as antidepressant 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, coma

Testing and check-ups: Your healthcare professional may do tests before you start, and during your treatment with AA-METHYLPHENIDATE SR. These tests may include:
- tests that check for problems in the heart or brain
- tests that check 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 you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Do NOT take AA-METHYLPHENIDATE SR if you are:

- Taking or have recently taken (within the past 14 days), a monoamine oxidase inhibitor (MAOI), used to treat depression. It may cause serious side effects.
- Taking clonidine (a medicine used to treat high blood pressure). It may cause serious side effects including sudden death.

If you are unsure, ask your healthcare professional.

The following may also interact with AA-METHYLPHENIDATE SR:

- alcohol
- medicines used to lower blood pressure,
- medicines used to treat depression, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs),
- medicines used to prevent seizures, such as phenobarbital, diphenylhydantoin and primidone,
- medicines used to prevent blood clots (commonly called "blood thinners"), such as warfarin,
- medicines that influence the level of dopamine in the body, medicines used to treat Parkinson's disease or manage psychosis,
- 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.

AA-METHYLPHENIDATE SR may give a false positive result when testing for drug use. This includes testing used in sport.

How to take AA-METHYLPHENIDATE SR

- Take AA-METHYLPHENIDATE exactly as your healthcare professional has told you to.
- Take AA-METHYLPHENIDATE SR tablets by mouth with or without food.
- Swallow tablets whole, do NOT chew, crush, or divide the tablets.

Usual dose:

Your healthcare professional will determine how much and how often you should take AA-METHYLPHENIDATE SR according to your individual needs. In order for you to receive the most benefits from AA-METHYLPHENIDATE SR, it is important that AA-METHYLPHENIDATE SR be taken only as directed by the healthcare professional.

Do not take more than 60 mg of AA-METHYLPHENIDATE SR per day.

Overdose:

If you think you, or a person you are caring for, have taken too much AA-METHYLPHENIDATE SR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If a dose of AA-METHYLPHENIDATE SR is missed, 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 AA-METHYLPHENIDATE SR to make up the missed dose. If you have any questions about this, check with the healthcare professional.

Possible side effects from using AA-METHYLPHENIDATE SR:

These are not all the possible side effects you may have when taking AA-METHYLPHENIDATE SR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- trouble sleeping
- dizziness
- feeling tired
- feeling anxious, nervous or jittery
- loss of appetite
- weight loss, weight gain
- stomach discomfort, nausea (feeling sick), vomiting, diarrhea
- increased sweating
- dry mouth
- fast heart rate
- difficulty opening the mouth (trismus)
- lack of bladder control (incontinence)
- swelling of the breasts in boys or men

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this 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			
Eye problems: eyesight changes or blurred vision, abnormal blinking or eyelid spasms		✓	
Very rare			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
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			✓
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		✓	
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			✓
Choreo-athetoid movements: uncontrollable writhing movements of the limb, face and/or trunk		✓	
Exfoliative dermatitis: skin blisters or itching			✓
Erythema multiforme: red blotches on the skin		✓	
Hallucinations: seeing or feeling things that are not really there			✓
Neuroleptic Malignant Syndrome: sudden high fever, very high blood pressure and severe convulsions			✓
Low white blood cell count: sore throat and fever or chills	✓		
Seizures or convulsions (fits): uncontrollable shaking with or without loss of consciousness			✓
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Tourette's Syndrome: motor tics (hard-to-control, repeated twitching of any part of the child's body) and verbal tics (hard-to			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
control repeating of sounds or words)			
Unknown			
Aggressive Behaviour or Hostility		✓	
Bladder infection: increased need to urinate, pain when urinating, blood in the urine		✓	
New or worsening mental health problems: paranoia, delusions - Hallucinations: seeing, feeling or hearing things that are not real - Mania: feeling unusually excited, over-active, or uninhibited		✓	
Nosebleed	✓		
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 suicide or hurting yourself (including completed suicide).			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store between 15°C - 30°C. Protect AA-METHYLPHENIDATE SR from moisture and heat.

AA-METHYLPHENIDATE SR tablets should not be used after the expiry date shown on the package label. Return any unused medicine to your pharmacist.

Keep out of reach and sight of children.

If you want more information about AA-METHYLPHENIDATE SR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/); or by calling 1-877-998-9097.

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