

PRESCRIBING INFORMATION

◇ RITALIN*
(methylphenidate hydrochloride)
10 mg and 20 mg tablets
Novartis Standard

◇ RITALIN* SR
(methylphenidate hydrochloride extended-release tablets)
20 mg tablets
Novartis Standard

Central Nervous System Stimulant

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Dorval, Quebec
H9S 1A9

Date of Preparation:
August 31, 1984
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December 10, 2007

Control No. 114929

◇ RITALIN* is a registered trademark

RITALIN*

(methylphenidate hydrochloride)

Novartis Standard

RITALIN* SR*

(methylphenidate hydrochloride extended-release tablets)

Novartis Standard

Therapeutic Classification

Central Nervous System Stimulant

Actions And Clinical Pharmacology

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

RITALIN* (methylphenidate hydrochloride) 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.

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.

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.

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 (V_{ss}) 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 (α -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 in the extended-release tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the RITALIN* SR tablet, compared to the RITALIN* tablet, measured by the urinary excretion of the methylphenidate major metabolite (PPAA), was 105% (49-168%) in children and 101% (85%-152%) in adults. The time to peak rate in children was 4.7 hours (1.3-8.2 hours) for the extended-release tablets and 1.9 hours (0.3-4.4 hours) for the regular tablets. 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.

Indications And Clinical Use

1. RITALIN* (methylphenidate hydrochloride) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, "on the go", excessive talking, blurting answers, can't wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and

evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

RITALIN* 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 physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

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

2. Narcolepsy

Contraindications

Anxiety, tension, agitation, thyrotoxicosis, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, glaucoma and pheochromocytoma. Known or suspected hypersensitivity to the drug or its excipients. Also contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Monoamine Oxidase Inhibitors

RITALIN* is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

Warnings

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, RITALIN* and RITALIN* SR generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

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, 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).

Misuse and Cardiovascular events

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

Hypertension and other Cardiovascular Conditions

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, heart failure, recent myocardial infarction, or ventricular arrhythmia (see also WARNINGS and CONTRAINDICATIONS).

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.

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 RITALIN*. 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 RITALIN* (see above, Cardiovascular, and PRECAUTIONS, Drug Interactions).

Psychiatric conditions

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Treatment of ADHD with stimulant products including RITALIN* 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.

In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, RITALIN* should not be given to patients unless the benefit outweighs the potential risk.

Psychotic symptoms

Psychotic symptoms, including visual and tactile hallucinations have been reported in patients administered usual prescribed doses of stimulant products, including RITALIN* (see ADVERSE REACTIONS). Physicians should consider treatment discontinuation.

Bipolar Illness

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.

Aggressive behaviour

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including RITALIN*. However, patients with ADHD may experience aggression as part of their medical condition. Therefore causal association with treatment is difficult to assess. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

Patients with emergent suicidal ideation and behaviour during treatment for ADHD should be evaluated immediately by their physician. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Depression

RITALIN* should not be used to treat severe exogenous or endogenous depression.

Use in Children Under Six Years of Age

RITALIN* (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.

Endocrine and Metabolism

Long-Term Suppression of Growth

Although a causal relationship has not been established, suppression of growth (i.e., weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. 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.

Fatigue

RITALIN* should not be used for the prevention or treatment of normal fatigue states.

Neurologic

Seizures

There is some clinical evidence that RITALIN* 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 RITALIN*. If seizure frequency rises, the drug should be discontinued.

Ophthalmologic

Visual Disturbance

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

Usage In Pregnancy And Lactation

Pregnancy: Studies to establish safe use of methylphenidate in pregnant women have not been conducted. Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day. The systemic exposure in rabbit at this dose is 5.1 times that in humans at the maximum recommended human dose (60 mg).

Therefore, RITALIN* should not be given to pregnant women unless the potential benefit outweighs the risk to fetus.

Lactation: It is not known whether the active substance of RITALIN* and/or its metabolites pass into the breast milk. For safety reasons, the physician should assess the patient's medical condition and advise one of the following options: refrain from breast-feeding their infants while taking RITALIN*, or discontinue the drug while nursing.

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

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 as well as the effects of chronic over activity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

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

Precautions

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

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of Attention Deficit Hyperactivity Disorder and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe RITALIN* (methylphenidate hydrochloride) should depend on the physician'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 RITALIN* is usually not indicated.

Long-term effects of RITALIN* in children have not been well established.

Because RITALIN* may affect performance, patients should be cautioned against engaging in hazardous activities (i.e., operation of automobiles or dangerous machinery).

Drug Interactions

Pharmacodynamic interactions

RITALIN* may decrease the effectiveness of drugs used to treat hypertension. Use with caution in patients being treated with drugs that elevate blood pressure including MAO inhibitors (see also WARNINGS, Cerebrovascular Conditions).

As an inhibitor of dopamine reuptake, RITALIN* may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g. haloperidol). The coadministration of RITALIN* with antipsychotics is not recommended because of the counteracting mechanism of action.

Case reports suggested a potential interaction of RITALIN* with coumarin anticoagulants, some anticonvulsants (e.g. phenobarbital, diphenylhydantoin, primidone), phenylbutazone and tricyclic antidepressants but pharmacokinetic interactions were not confirmed when explored at higher sample sizes. Downward dosage adjustments of these drugs might be required when given concomitantly with RITALIN*.

Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including RITALIN*. Therefore, patients should be advised to abstain from alcohol during treatment.

Pharmacokinetic interactions

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

RITALIN* coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

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

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

Other

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

Clonidine

Serious adverse events have been reported in concomitant racemic methylphenidate use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Adverse Reactions

Frequency estimate: very common $\geq 10\%$, common $\geq 1\%$ to $< 10\%$; uncommon $\geq 0.1\%$ to $< 1\%$; rare $\geq 0.01\%$ to $< 0.1\%$; very rare $< 0.01\%$

Nervousness and insomnia are very common adverse reactions which occur at the beginning of RITALIN* treatment, but can usually be controlled by reducing dosage and/or omitting the afternoon or evening dose. Decreased appetite is also common but usually transient.

Central And Peripheral Nervous System

Common: dizziness, drowsiness, headache, dyskinesia.

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

Very rare: hyperactivity, convulsions, muscle cramps, choreoathetoid movements, tics, or exacerbation of existing tics, transient depressed moods, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents, Tourette's syndrome, psychosis (sometimes with visual and tactile hallucinations).

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

Gastrointestinal System

Common: nausea, vomiting and abdominal pain may occur at the start of treatment and may be alleviated if taken with food. Dry mouth.

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

Cardiovascular System

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

Rare: Angina pectoris.

Skin And/Or Hypersensitivity Reactions

Common: rash, pruritus, urticaria, fever, arthralgia, scalp hair loss.

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

Hematologic System

Very rare: leukopenia, thrombocytopenia, anemia.

Miscellaneous

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

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

Post-Market Adverse Events

Adverse events reported since market introduction in patients taking RITALIN* include sudden cardiac death, suicide, suicidal ideation, suicide attempt, Stevens-Johnson Syndrome, pancreatitis, aplastic anaemia, hypoglycaemia, and transient pancytopenia. No causal relationship between RITALIN* and these events has been established.

Adverse Events 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 neuroleptic malignant syndrome (NMS) have been received, and in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

Symptoms And Treatment Of Overdosage

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system 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 and dryness of mucous membranes.

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. Airway protected gastric lavage is necessary in hyperactive or unconscious patients, or those with depressed respiration.

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 RITALIN* (methylphenidate hydrochloride) overdose has not been established.

Dosage And Administration

RITALIN* 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.

RITALIN* should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (see CONTRAINDICATIONS and WARNINGS).

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).

Caution should be exercised in prescribing concomitant drugs.

Dosage of RITALIN* (methylphenidate hydrochloride) should be individualized according to the needs and responses of the patient.

Children (6 Years And Over)

RITALIN* Tablets: RITALIN* 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.

Daily dosage above 60 mg is not recommended.

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.

RITALIN* SR (extended-release) Tablets: RITALIN* SR tablets have a duration of action of approximately 8 hours. Therefore, RITALIN* SR tablets may be used in place of RITALIN* tablets when the 8-hour dosage of RITALIN* SR corresponds to the titrated 8-hour dosage of RITALIN*. RITALIN* SR tablets must be swallowed whole and never be crushed or chewed.

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

RITALIN* 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.

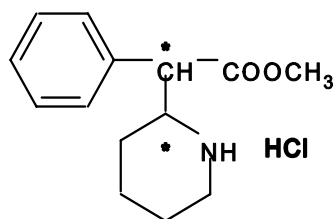
Adults

RITALIN* 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.

RITALIN* SR (extended-release) Tablets: RITALIN* SR tablets have a duration of action of approximately 8 hours. Therefore, RITALIN* SR tablets may be used in place of RITALIN* tablets when the 8-hour dosage of RITALIN* SR corresponds to the titrated 8-hour dosage of RITALIN*. RITALIN* SR tablets must be swallowed whole and never be crushed or chewed.

Pharmaceutical Information

Drug Substance



methylphenidate hydrochloride

Chemical name: a-Phenyl-2-piperidineacetic acid methyl ester hydrochloride
Molecular formula: C₁₄H₁₉NO₂HCl
Molecular weight: 269.8
Description: white, odorless, fine crystalline powder, solutions which are acid to litmus
Solubility: Freely soluble in water

Composition

RITALIN* (methylphenidate hydrochloride) 10 mg Tablets

Each tablet contains medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: corn starch, FD&C Green No. 3, lactose, magnesium stearate, polyethylene glycol, sugar and talc.

RITALIN* (methylphenidate hydrochloride) 20 mg Tablets

Each tablet contains the medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: D&C Yellow No. 10, lactose, magnesium stearate, polyethylene glycol, sugar, tragacanth and talc.

RITALIN* (methylphenidate hydrochloride) 20 mg SR Tablets

Each tablet contains the medicinal ingredient methylphenidate hydrochloride and non-medicinal ingredients: cellulose compounds, cetostearyl alcohol, castor oil compounds, lactose, magnesium stearate, talc and titanium dioxide.

Stability And Storage Recommendations

Protect from heat (store between 2 and 30⁰C) and humidity.

Keep out of reach and sight of children.

Availability Of Dosage Forms

RITALIN* (methylphenidate hydrochloride) Tablets 10 mg

Pale blue, round, flat-faced, bevel-edged tablets that are scored and imprinted "AB" on one side with "CIBA" on the other.

RITALIN* (methylphenidate hydrochloride) Tablets 20 mg

Pale yellow, round, flat-faced, bevel-edged tablets that are scored and imprinted "PN" on one side with "CIBA" on the other.

RITALIN* SR 20 mg (methylphenidate hydrochloride extended-release tablets)

White, round, biconvex, film-coated tablets that have "16" printed on one side with "CIBA" printed on the other in black ink.

RITALIN* 10 and 20 mg tablets are packaged in bottles of 100 and 500.

RITALIN* SR 20 mg tablets are packaged in bottles of 100.

RITALIN* is a controlled drug (Schedule G).

Toxicology

Pregnancy-embryonal/fetal development

Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day. The systemic exposure in rabbit at this dose is 5.1 times that in human at the maximum recommended human dose (60 mg). Spina bifida with malrotated hind limb was observed in 2 (out of 18) litters.

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/m² 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 RITALIN*, there is no evidence that the incidence is higher in patients receiving RITALIN*.

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/m² 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 neurobehavioural 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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