NOVARTIS

Methylphenidate hydrochloride

Ritalin® / Ritalin® LA

Psychostimulant / Psychoanaleptics (Centrally-acting Sympathomimetics)

DESCRIPTION AND COMPOSITION

Active substance

Tablet: Each divisible, immediate-release tablet contains 10 mg methylphenidate hydrochloride.

LA Capsule: Each modified-release capsule contains 20 mg, 30 mg and 40 mg methylphenidate hydrochloride.

Active moiety

Methylphenidate (INN for alpha-phenyl-2-piperidine acetic acid methyl ester).

Excipients

Tablet: calcium phosphate, lactose, wheat starch, gelatin, magnesium stearate, talc.

LA capsule [20 mg, 30 mg, and 40 mg]: ammonio methacrylate copolymer, black iron oxide (E172) (40 mg capsule only), gelatin, methacrylic acid copolymer, macrogol, red iron oxide (E172) (40 mg capsule only), sugar spheres, talc, titanium dioxide (E171), triethyl citrate, yellow iron oxide (E172) (30 mg and 40 mg capsules only).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV)

Methylphenidate (Ritalin®) is indicated in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years or older.

Methylphenidate (Ritalin® LA) is indicated in the treatment of ADHD in children aged 6 years or older, and in adults.

ADHD was previously known as attention-deficit disorder or minimal brain dysfunction. Other terms used to describe this behavioral syndrome include: hyperkinetic disorder, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of patients. Methylphenidate (Ritalin®) is indicated as part of a comprehensive treatment program which typically includes psychological, educational, and social measures and is aimed at stabilizing patients with a behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10. Non-localizing (soft) neurological signs, learning disability, and

abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations for ADHD in children

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Proper diagnosis requires medical and neuropsychological, educational, and social investigation. Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity, minor neurological signs, and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics. Drug treatment is not indicated in all children with this syndrome. Stimulants are not indicated in children with symptoms secondary to environmental factors (child abuse in particular) and/or primary psychiatric disorder, including psychosis. Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms.

Special Diagnostic Considerations for ADHD in adults

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adults with ADHD have symptom patterns characterized by shifting activities, becoming bored easily, restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD. Diagnosis in adults should include a structured patient interview to determine current symptoms. The preexistence of childhood ADHD is to be determined retrospectively. Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment of the severity and chronicity of the symptoms and their impact on the daily life of the patient.

Narcolepsy [Tablet only]

Symptoms include daytime sleepiness, inappropriate sleep episodes, and sudden loss of voluntary muscle tone.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Dosage should be individualized according to the patient's clinical needs and responses.

In the treatment of ADHD, an attempt should be made to time administration to coincide with the periods of greatest academic, behavioral, or social stress.

Methylphenidate (Ritalin®) should be started at a low dose, with increments at weekly intervals.

Daily doses above 60 mg are not recommended for the treatment of narcolepsy, or for the treatment of ADHD in children.

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults [methylphenidate (Riltalin®LA) capsules only].

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

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

If the effect of the drug wears off too early in the evening, disturbed behavior and/or inability to go to sleep may recur. A small evening dose of methylphenidate (Ritalin®) tablet may help to solve this problem.

Pre-treatment screening

Before initiating treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular arrhythmia and psychiatric disorders. Weight and height should also be measured before treatment and documented on a growth chart (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Periodic assessment of the treatment in ADHD

Drug treatment does not need to be indefinite. Physicians should periodically re-evaluate the treatment with trial periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

When used in children with ADHD, treatment can usually be discontinued during or after puberty.

ADHD

Children and adolescents (6 years and over)

Tablets

Start with 5 mg once or twice daily (e.g. at breakfast and lunch) with weekly increments of 5 to 10 mg. The total daily dosage should be administered in divided doses.

LA capsules

Methylphenidate (Ritalin® LA) modified-release capsule are for oral administration once daily in the morning. The recommended starting dose of is 20 mg.

A maximum daily dose of 60 mg should not be exceeded.

Adults

Only the modified-release formulation (LA capsules) should be used for the treatment of ADHD in adults.

Methylphenidate (Ritalin® LA) is administered once daily.

Patients new to methylphenidate (see section CLINICAL PHARMACOLOGY): The recommended starting dose in patients who are not currently taking methylphenidate is 20 mg once daily.

Patients currently using methylphenidate: Treatment may be continued with the same daily dose. If the patient was previously treated with an immediate release formulation, a switchto an appropriate recommended dose of methylphenidate (Ritalin® LA) should be made (see below subsection Switching patient's treatment to Methylphenidate (Ritalin® LA)).

A maximum daily dose of 80 mg should not be exceeded.

No difference in dosing is recommended between male and female adult patients (see section CLINICAL STUDIES).

Switching patient's treatment to LA capsules

The recommended dose of LA capsules should be equal to the total daily dose of the immediate-release formulation not exceeding a total dose of 60 mg in children and 80 mg in adults. Examples involving switch from the immediate-release formulation are provided below.

Table 1 Recommended daily dose when switching treatment from immediate-release tablet to modified-release capsules

Previous dose with immediate release tablet	Recommended dose with modified-release capsule
10 mg methylphenidate twice daily	20 mg once daily
15 mg methylphenidate twice daily	30 mg once daily
20 mg methylphenidate twice daily	40 mg once daily

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. The dosage of the modified-release capsules may be adjusted at weekly intervals in 10 mg increments for children and in 20 mg increments for adults.

Narcolepsy

Only the immediate-release tablet is approved in the treatment of narcolepsy in adults.

The average daily dose is 20 to 30 mg, given in 2 to 3 divided doses.

Some patients may require 40 to 60 mg daily, while for 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.

A maximum daily dose of 60 mg should not be exceeded.

Special populations

Renal impairment

No studies have been performed in renally impaired patients (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

No studies have been performed in hepatically impaired patients (see section CLINICAL PHARMACOLOGY).

Geriatric patients (65 years or above)

No studies have been performed in patients over 60 years of age (see section CLINICAL PHARMACOLOGY).

Method of administration

General recommendations

Tablet: Can be taken with or without food (see section CLINICAL PHARMACOLOGY).

LA capsules and/or their contents should not be crushed, chewed, or divided. They may be administered with or without food. They may be swallowed whole or alternatively may be administered by sprinkling the contents over a small amount of food (see specific instructions below).

Administration by sprinkling capsule contents on food

The capsules may be carefully opened and the beads sprinkled over soft food (e.g. applesauce). The food should not be warm because this could affect the modified-release properties of this formulation. The mixture of drug and food should be consumed immediately in its entirety. The drug and food mixture should not be stored for future use.

Methylphenidate (Ritalin® LA), administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate to the same total dose of methylphenidate (Ritalin®) administered twice daily.

CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or to any of the excipients.
- Anxiety, tension.
- Agitation.
- Hyperthyroidism.
- Pre-existing cardiovascular disorders including 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).
- During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 2 weeks of discontinuing those drugs, due to risk of hypertensive crisis (see section INTERACTIONS)
- Glaucoma.
- Phaeochromocytoma.
- Diagnosis or family history of Tourette's syndrome.

WARNINGS AND PRECAUTIONS

General

Treatment with methylphenidate is not indicated in all cases of Attention-Deficit/Hyperactivity disorder, and should be considered only after detailed history-taking and evaluation. The decision to prescribe methylphenidate should depend on an assessment of the severity of symptoms and, in pediatric patients, their appropriateness to the child's age, and not simply on the presence of one or more abnormal behavioral characteristics. Where these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Cardiovascular

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems: Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in patients with structural cardiac abnormalities or other serious problems. A causal relationship with stimulant products has not been established since some of these conditions alone may carry an increased risk of sudden death. Stimulant products, including methylphenidate, generally should not be used in patients with known structural cardiac abnormalities or other serious cardiac disorders that may increase the risk of sudden death due to sympathomimetic effects of a stimulant drug. Before initiating treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see section DOSAGE REGIMEN AND ADMINISTRATION).

Cardiovascular Conditions: Methylphenidate is contraindicated in patients with severe hypertension. Methylphenidate increases heart rate and systolic and diastolic blood pressure. Therefore, 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. Severe cardiovascular disorders are contraindicated (see section CONTRAINDICATIONS).

Blood pressure should be monitored at appropriate intervals in all patients taking methylphenidate, especially those with hypertension. Patients who develop symptoms suggestive of cardiac disease during treatment should undergo a prompt cardiac evaluation.

Misuse and Cardiovascular Events:

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

Cerebrovascular

Cerebrovascular conditions: Patients with pre-existing central nervous system (CNS) abnormalities, e.g., cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with methylphenidate. Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment (see above, paragraph on Cardiovascular Conditions and section INTERACTIONS).

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 methylphenidate, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section DOSAGE REGIMEN AND ADMINISTRATION).

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

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

Psychotic symptoms

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

Aggressive behavior

Emergent aggressive behavior or an exacerbation of baseline aggressive behavior has been reported during stimulant therapy, including methylphenidate. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioral changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

Patients and caregivers of patients should be alerted about the need to monitor for clinical worsening, suicidal behavior or thoughts or unusual changes in behavior and to seek medical advice immediately if these symptoms appear. The physician should initiate appropriate treatment of any underlying psychiatric condition and consider a possible discontinuation or change in the ADHD treatment.

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see section ADVERSE DRUG REACTIONS). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of methylphenidate for ADHD treatment. Methylphenidate is contraindicated in case of diagnosis or family history of Tourette's syndrome (see section CONTRAINDICATIONS). Patients should be regularly monitored for the emergence or worsening of tics during treatment.

Serotonin syndrome

Serotonin syndrome has been reported following co-administration of methylphenidate was co-administered with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome. The symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Prompt recognition of these symptoms is important so that treatment with methylphenidate and serotonergic drugs can be immediately discontinued and appropriate treatment instituted (see section INTERACTIONS).

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism generally developed after some time on the drug, often subsequent to an increase in dose. Priapism has also been reported during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Growth retardation

Moderately reduced weight gain and slight growth retardation have been reported with the long-term use of stimulants, including methylphenidate, in children (see section ADVERSE DRUG REACTIONS). Growth should be monitored as clinically necessary during treatment and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

Methylphenidate should be used with caution in patients with epilepsy as clinical experience has shown that it can cause an increase in seizure frequency in a small number of such patients. If seizure frequency increases, treatment should be discontinued.

Drug abuse and dependence

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes may occur, especially with parenteral abuse. Clinical data indicate that children given methylphenidate are not more likely to abuse drugs as adolescents or adults.

Caution is called for in emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because they may increase the dosage on their own initiative

Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as the effects of chronic overactivity. Some patients may require long-term follow-up.

Hematological effects

The long-term safety and efficacy profiles of methylphenidate are not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. In the event of hematological disorders appropriate medical intervention should be considered (see section ADVERSE DRUG REACTIONS)

Pediatric patients under 6 years of age

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

Driving and using machines

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

ADVERSE DRUG REACTIONS

Nervousness and insomnia are very common adverse reactions which occur at the beginning of treatment but can usually be controlled by reducing the 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.

Tabulated summary of adverse drug reactions

Adverse drug reactions (Table 2) are listed by MedDRA 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 for each adverse drug reaction is

based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse reactions reported with methylphenidate use from clinical studies, spontaneous reports and literature

Infections and infestations	
Very common:	Nasopharyngitis*
Blood and the lymphatic system disorders	
Very rare:	Leucopenia, thrombocytopenia, anemia
Immune system disorders	
Very rare:	Hypersensitivity reactions including angioedema and anaphylaxis
Metabolism and nutrition disorders	
Very common:	Decreased appetite**
Rare:	Moderately reduced weight gain during prolonged use in children
Psychiatric disorders	
Very common:	Nervousness, insomnia
Common:	Anxiety*, restlessness*, sleep disorder*, agitation*, depression, aggression, bruxism*
Very rare:	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood
Nervous system disorders	
Common:	Dyskinesia, tremor*, headache, drowsiness, dizziness.
Very rare:	Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral hemorrhages and cerebrovascular accidents
Eye disorders	
Rare:	Difficulties in visual accommodation, blurred vision
Cardiac disorders	
Common:	Tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase)
Rare:	Angina pectoris
Respiratory, thoracic and mediastinal disorders	
Common:	Cough*
Gastrointestinal disorders	

Very common:	Nausea**, dry mouth**
Common:	Abdominal pain, vomiting, dyspepsia*, toothache*
Hepatobiliary disorders	
Very rare:	Abnormal liver function, ranging from transaminase elevation to hepatic coma
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, urticaria, fever, scalp hair loss, hyperhidrosis*.
Very rare:	Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia
Uncommon:	Trismus*
Very rare:	Muscle cramps
General disorders and administration site conditions	
Common:	Feeling jittery*
Rare:	Slight growth retardation during prolonged use in children
Investigations	
Common:	Weight decreased*
Vasular disorders	
Common:	Raynaud's phenomenon**, peripheral coldness**

* ADRs reported from the clinical trials performed in adult ADHD patients.
** The reported frequency of ADRs was based on the frequency observed in the adult ADHD clinical studies which was higher than that previously reported for children.

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 methylphenidate played in these cases.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with methylphenidate via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 3 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Reproductive system and breast disorders
Priapism

Psychiatric disorders Dysphemia, suicidal ideation or attempt (including completed suicide)
Renal and urinary disorders Enuresis

Additional adverse reactions reported with other methylphenidate-containing products

The list below shows adverse reactions not listed for methylphenidate (see Table 2) that have been reported with other methylphenidate-containing products based on clinical studies data and post-marketing spontaneous reports.

Blood and lymphatic disorders: Pancytopenia

Immune system disorders: Hypersensitivity reactions such as auricular swelling

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

Nervous system disorders: Reversible ischemic neurological deficit, migraine

Eye disorders: Diplopia, mydriasis, visual disturbance

Cardiac disorders: Cardiac arrest, myocardial infarction

Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain, dyspnea

Gastrointestinal disorders: Diarrhea, constipation

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders: Myalgia, muscle twitching

Renal and urinary disorders: Hematuria

Reproductive system and breast disorders: Gynecomastia

General disorders and administration site conditions: Chest pain, fatigue, sudden cardiac death

Investigations: Cardiac murmur

INTERACTIONS

Pharmacodynamic interactions

Anti-hypertensive drugs

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure

Methylphenidate should be used with caution in patients being treated with drugs that elevate blood pressure (see also paragraph on Cerebrovascular Conditions in section WARNINGS AND PRECAUTIONS).

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors (see section CONTRAINDICATIONS).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with anesthetics

There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, methylphenidate should not be taken on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)

Serious adverse events including sudden death, have been reported in concomitant use with clonidine, although no causality for the combination has been established.

Use with serotonergic drugs

The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome (see section WARNINGS AND PRECAUTIONS). Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Use with dopaminergic drugs

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

Pharmacokinetic interactions

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

Co-administration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports suggested a potential interaction with coumarin anticoagulants, some anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic antidepressants but pharmacokinetic interactions were not confirmed when explored at larger sample sizes. The dosage of these drugs might have to be reduced.

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

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

Drug/Laboratory test

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is insufficient experience with use of methylphenidate in pregnant women. Methylphenidate should not be given to pregnant women unless the potential benefit outweighs the risk to the fetus. Methylphenidate is potentially teratogenic in rabbits

Animal data

Methylphenidate is considered to be possibly teratogenic in rabbits. Spina bifida with malrotated hind limbs was observed in two separate litters at a dose of 200 mg/kg/day. Exposure (AUC) at this dose was approximately 5.1 times higher than the extrapolated exposure at the MRHD. Exposure at the next lower dose, wherein no spina bifida was found, was 0.7 times the extrapolated exposure at MRHD.A second study was conducted with a high dose of 300 mg/kg, which was considered maternally toxic. No spina bifida was seen in 12 litters (92 fetuses) surviving. Exposure (AUC) at 300 mg/kg was 7.5 times the extrapolated exposure at MRHD.

Methylphenidate is not teratogenic in rats. Development of fetal toxicity was noted at a high dose of 75 mg/kg (20.9 times higher than the exposure (AUC) at MRHD) and consisted of an increase of the instance of fetuses with delayed ossification of the skull and hyoid bones as well as fetuses with short supernumerary ribs.

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis), offspring body weight gain was decreased at the highest dose, but no other effects on postnatal development were observed.

Lactation

Risk summary

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

A decision should be made whether to abstain from breast-feeding or to abstain from methylphenidate therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Females and males of reproductive potential

There are no data to support special recommendation in women of child-bearing potential.

Infertility

No human data on the effect of methylphenidate on fertility are available. Methylphenidate did not impair fertility in male or female mice (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Signs and symptoms

Signs and symptoms of acute overdosage, mainly due to overstimulation of the central and sympathetic nervous systems, may include: vomiting, agitation, tremor, hyperreflexia, muscle twitching, convulsions (possibly followed by coma), euphoria, confusion, hallucinations, delirium,

sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Management

When treating an overdose, practitioners should bear in mind that a second release of methylphenidate from the modified-release capsules occurs approximately four hours after administration.

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.

Supportive 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, the stomach could be evacuated by induction of vomiting, 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.

The efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate overdosage has not been established. Clinical experience with acute overdosage is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcemia, reversal may be achieved with supplemental oral calcium and/or an infusion of calcium gluconate.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)/ Pharmacodynamics (PD)

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

Methylphenidate is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in humans is not completely understood, but its stimulant effects are thought to be due to an inhibition of dopamine and norepinephrine reuptake into presynaptic neurons and thereby increasing these neurotransmitters in the extraneuronal space.

The mechanism by which methylphenidate exerts its mental and behavioral effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system.

The l-enantiomer is thought to be pharmacologically inactive.

The effect of treatment with 40 mg dexmethylphenidate hydrochloride, the pharmacologically active d-enantiomer, on QT/QTc interval was evaluated in a study in 75 healthy volunteers. The maximum mean prolongation of QTcF intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and no exposure response relationship was evident.

Pharmacokinetics (PK)

Absorption

Tablets

After oral administration the active substance (methylphenidate hydrochloride) is rapidly and almost completely absorbed. Owing to extensive first-pass metabolism, the absolute bioavailability was 22±8 % for the d-enantiomer and 5±3 % for the l-enantiomer. Ingestion with food has no relevant effect on the rate of absorption. Peak plasma concentrations of about 40 nmol/L (11 ng/mL) are reached on average 1 to 2 hours after administration. Peak plasma concentrations vary markedly between patients. The area under the concentration-time curve (AUC), and the peak plasma concentration (C_{max}) are proportional to the dose.

LA capsules

Following oral administration of methylphenidate modified-release capsules (Ritalin® LA) to children diagnosed with ADHD and adults, methylphenidate is rapidly absorbed and produces a bi-modal plasma concentration-time profile (i.e. two distinct peaks approximately four hours apart). The relative bioavailability of the LA capsules given once daily is comparable to the same total dose of methylphenidate immediate release tablets given twice a day in children and in adults.

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for the modified-release capsule given once a day compared to the immediate release tablets given twice a day.

Food Effects

The capsules may be administered with or without food. There were no differences in its bioavailability when administered with either a high-fat breakfast or applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the capsule, the contents may be sprinkled on soft food such as applesauce and administered (see section DOSAGE REGIMEN AND ADMINISTRATION).

Distribution

In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Binding to plasma proteins is low (10 to 33%). The volume of distribution was 2.65±1.11 L/kg for d-MPH and 1.80±0.91 L/kg for l-MPH.

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. Adverse events were not noted in either infant (6 and 11 months of age).

Biotransformation/metabolism

Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Peak plasma concentrations of the main, deesterified, metabolite - alpha-phenyl-2-piperidine acetic-acid (ritalinic acid) - are attained about 2 hours after administration and are 30 to 50 times higher than those of the unchanged substance. The elimination half-life of alpha-phenyl-2-piperidine acetic acid is about twice that of methylphenidate, and its mean systemic clearance is 0.17 L/h/kg. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

Elimination

Methylphenidate is eliminated from the plasma with a mean elimination half-life of 2 hours. The systemic clearance is 0.40±0.12 L/h/kg for d-MPH and 0.73±0.28 L/h/kg for l-MPH. After oral administration, 78 to 97% of the dose is excreted in urine and 1 to 3 % in feces in the form of metabolites within 48 to 96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in urine. Most of the dose is excreted in the urine as alpha-phenyl-2-piperidine acetic acid (60 to 86 %).

Special populations

Effect of age: There are no apparent differences in the pharmacokinetics of methylphenidate between hyperactive children (6-13 years) and healthy adult volunteers.

Patients with renal impairment: Elimination data from patients with normal renal function suggest that renal excretion of unchanged methylphenidate would hardly be diminished in the presence of impaired renal function. However, renal excretion of the metabolite alpha-phenyl-2-piperidine acetic acid may be reduced.

CLINICAL STUDIES

Methylphenidate has been used for over 50 years in the treatment of ADHD. Its effectiveness in the treatment of ADHD is well established. In addition to improving core symptoms of ADHD, methylphenidate also improves behaviors associated with ADHD such as impaired academic performance and social function.

Studies in the published literature have shown methylphenidate to significantly improve daytime sleepiness and cataplexy.

Children with ADHD

Methylphenidate (Ritalin® LA) was evaluated in a randomized, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) received a single morning dose of methylphenidate (Ritalin® LA) in the range of 10-40 mg/day, or placebo, for up to 2 weeks. The optimal dose for each patient was determined in a dose titration phase of the study prior to randomization.

The primary efficacy variable was the change from baseline to the final rating in the ADHD/DSM-IV Scale for Teachers (CADS-T) total subscale score. CADS-T assesses symptoms of hyperactivity and inattention. The analysis of the primary efficacy variable showed a significant treatment difference in favor of methylphenidate (Ritalin® LA) ($p<0.0001$). A statistically significant treatment effect for methylphenidate (Ritalin® LA) relative to placebo was also found in all analyses of the secondary CADS efficacy variables, as well as in two post-hoc analyses for the ADHD diagnostic subtypes (combined type, inattentive type). The results of the primary and secondary efficacy analyses are summarized in Table 4.

Table 4 ADHD/DSM-IV Subscales for teachers and parents, change from baseline (ITT population, LOCF analysis)

	Methylphenidate (Ritalin® LA)		**Placebo**		
	n	Mean change[1] (SD[2])	n	Mean change[1] (SD[2])	p-value
CADS-T subscale					
Total	62[3]	10.7 (15.7)	70[3]	-2.8 (10.6)	< 0.0001

	Methylphenidate (Ritalin® LA)		Placebo		
Inattentive	62	5.3 (8.25)	70	-1.5 (5.67)	< 0.0001
Hyperactive-Impulsive	62	5.4 (7.95)	70	-1.3 (5.93)	< 0.0001
CADS-P subscale					
Total	63	6.3 (13.5)	70	0.5 (13.55)	0.0043
Inattentive	63	2.8 (7.28)	70	0.2 (6.4)	0.0213
Hyperactive-Impulsive	63	3.5 (6.87)	70	0.3 (7.66)	0.0015

[1]score at end of placebo-washout period minus final score

[2]standard deviation

[3]two patients (one in each treatment group) had no CADS-T baseline values but had post-randomization values. They are, therefore, not included in the descriptive statistics.

Adults with ADHD

Methylphenidate (Ritalin® LA) was evaluated in a randomized, double-blind, placebo-controlled, multicentre study (RIT124D2302) in the treatment of 725 adult patients (395 male and 330 female) diagnosed with ADHD according to DSM-IV ADHD criteria. The study was designed to:

1) Confirm the clinically effective and safe dose range of methylphenidate (Ritalin® LA) for adults (18 to 60 years old) in a 9-week, double-blind, randomized, placebo-controlled, parallel group period (Period 1) consisting of a 3-week titration stage followed by a 6-week fixed dose stage (40, 60, 80 mg/day or placebo). Subsequently patients were re-titrated to their optimal dose of methylphenidate (Ritalin® LA) (40, 60 or 80 mg/day) over a 5 week period (Period 2).

2) Evaluate the maintenance of effect of methylphenidate (Ritalin® LA) in adults with ADHD in a 6-month, double-blind, randomized, withdrawal study (period 3). Efficacy was assessed using the DSM-IV ADHD rating scale (DSM-IV ADHD RS) for symptomatic control and Sheehan Disability Score (SDS) for functional improvement as change in respective total scores from baseline to the end of the first period. All dose levels of methylphenidate (Ritalin® LA) showed significantly greater symptom control ($p<0.0001$ for all dose levels) compared to placebo as measured by a reduction in DSM-IV ADHD RS total score. All doses of methylphenidate (Ritalin® LA) showed significantly greater functional improvement ($p=0.0003$ at 40 mg, $p=0.0176$ at 60 mg, $p<0.0001$ at 80 mg) compared to placebo as measured by reduction in SDS total score (see Table 5).

Significant clinical efficacy was demonstrated at all three methylphenidate (Ritalin® LA) dose levels using physician rated scales [Clinical Global Impression- Improvement (CGI-I) and Clinical Global Improvement- Severity (CGI-S)], self-rated scales [Adult Self-Rating Scale (ASRS)] and observer-rated scales [Conners' Adult ADHD Rating Scale Observer Short Version (CAARS O: S)]. The results were consistently in favor of methylphenidate (Ritalin® LA) over placebo across all assessments in period 1.

Table 5 Analysis of improvement from baseline 1 to end of Period 1 in DSM IV ADHD RS total score and SDS total score by treatment / (LOCF*) for Period 1

		Methylphenidate (Ritalin® LA) 40 mg	Methylphenidate (Ritalin® LA) 60 mg	Methylphenidate (Ritalin® LA) 80 mg	Placebo
Change in DSM- IV	N	160	155	156	161
	LS mean*	15.45	14.71	16.36	9.35

		Methylphenidate (Ritalin® LA) 40 mg	Methylphenidate (Ritalin® LA) 60 mg	Methylphenidate (Ritalin® LA) 80 mg	Placebo
ADHD RS from baseline	p- value	<0.0001	<0.0001	<0.0001	
	Significance level	0.0167	0.0208	0.0313	
Change in SDS total score from baseline	N	151	146	148	152
	LS mean	5.89	4.9	6.47	3.03
	p-value	0.0003	0.0176	<0.0001	
	Significance level***	0.0167	0.0208	0.0313	

* LOCF – Last Observation Carried Forward using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1, **LS mean- Least Square mean changes from Analysis of Covariance (ANCOVA) model with treatment group and center as factors and baseline DSM-IV ADHD RS total score and SDS total score as covariate, ***Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure

Maintenance of effect of methylphenidate (Ritalin® LA) was evaluated by measuring the percentage of treatment failure in methylphenidate (Ritalin® LA) compared to the placebo group at the end of a 6-month maintenance period (see Table 6). Once the methylphenidate (Ritalin® LA) dose was optimized in Period 2, approximately 79% of patients continued to maintain disease control for a period of at least 6 months (p <0.0001 vs. placebo). An odds ratio of 0.3 suggested that patients treated with placebo had a 3 times higher chance of becoming a treatment failure compared to methylphenidate (Ritalin® LA).

Table 6 Percentage of treatment failures during Period 3

			All methylphenidate (Ritalin® LA) vs placebo	
	All Methylphenidate (Ritalin® LA) N=352 n (%)	Placebo N=115 n (%)	Odds ratio (95% CI)	P-value* (significance level**)
Treatment failure	75 (21.3)	57 (49.6)	0.3 (0.2, 0.4)	<0.0001 (0.0500)
Not treatment failure	277 (78.7)	58 (50.4)		

* Two-sided p-value based on comparison between each methylphenidate (Ritalin® LA) group and placebo using the logistic regression model.

**Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure

Patients who entered Period 3 had completed a total of between 5-14 weeks of methylphenidate (Ritalin® LA) treatment in Periods 1 and 2. Patients then assigned to placebo in Period 3 did not experience increased signs of withdrawal and rebound compared to patients who continued on methylphenidate (Ritalin® LA) treatment.

The study performed in adults did not suggest any difference in efficacy or safety amongst gender subgroups (see section DOSAGE REGIMEN AND ADMINISTRATION).

The long term efficacy and safety of methylphenidate (Ritalin® LA) in adult patients was further evaluated in a 26-week open label extension study of methylphenidate (Ritalin® LA) in 298 adult patients with ADHD (RIT124D2302E1). Combining all patients in both studies, a total of 354 patients continuously received methylphenidate (Ritalin® LA) for > 6 months and 136 patients for > 12 months.

The safety profile of methylphenidate (Ritalin® LA) did not change with the longer duration of treatment of adult ADHD patients. The safety profile seen in study RIT124D2302E1 was similar to that observed in study RIT124D2302. No unexpected serious adverse events or adverse events were observed in this extension study and the commonly observed adverse events were expected and driven by the pharmacologic activity.

Furthermore, methylphenidate (Ritalin® LA) treatment during the study consistently demonstrated clinical efficacy when using self-rated scales (SDS) and physician-rated scales (ie, DSM-IV ADHD RS, CGI-I, and CGI-S). The results were consistently in favor of methylphenidate (Ritalin® LA) treatment across all assessments. Patients continued to show symptomatic improvement and a reduction in functional impairment throughout the study as shown by the mean change in DSM-IV ADHD total score by -7.2 points and the mean change in SDS total score by -4.8 points when assessed against the extension baseline.

NON-CLINICAL SAFETY DATA

Reproductive toxicity

See section PREGNANCY, LACTATION AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted over two generations of mice continuously receiving methylphenidate doses of up to 160 mg/kg/day (about 90-fold higher than the MRHD on a mg/kg basis).

Carcinogenicity

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas (a benign tumor) and, in males only, an increase in hepatoblastomas (a malignant tumor) at daily doses of approximately 60 mg/kg/day about 35-fold-higher than the maximum recommended human dose (MRHD) on a mg/kg basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no overall increase in the number of malignant hepatic tumors. The mouse strain used is particularly sensitive to the development of hepatic tumors. It is thought that hepatoblastomas might be due to non-genotoxic mechanisms such as an increase in hepatic cell proliferation. This is consistent with the increase in liver weights observed in this mouse carcinogenicity study.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis).

Genotoxicity

With methylphenidate, sister chromatid exchange and chromosome aberrations were elevated in one *in vitro* study in Chinese Hamster Ovary (CHO) cells. However, no genotoxicity effects were seen in several other assays, including no mutagenic effects in three *in vitro* tests (Ames reverse mutation

test, mouse lymphoma forward mutation test, human lymphocyte chromosome aberration test) and no evidence of clastogenic or aneugenic effects in two *in vivo* mouse bone marrow micronucleus tests, at doses up to 250 mg/kg. B6C3F1 mice from the same strain that showed liver tumors in the cancer bioassay were used in one of these studies. Additionally, there was no genotoxic potential as assessed by measuring cII mutations in the liver and micronuclei in peripheral reticulocytes in the Big Blue mouse, micronuclei in peripheral blood reticulocytes, HPRT mutations and chromosomal aberrations in peripheral blood lymphocytes of rhesus monkeys, *Pig A* locus mutations in adolescent rats, micronucleated reticulocyte frequencies in blood and DNA damage in blood, brain, and liver cells of adult male rats treated for 28 consecutive days, and by measuring micronuclei in mouse peripheral blood erythrocytes.

Juvenile toxicity

In a conventional study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When the animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose of 100 mg/kg/day (about 58-fold higher than the MRHD on a mg/kg basis). The clinical relevance of these findings is unknown.

INCOMPATIBILITIES

Not applicable.

STORAGE

Store at temperatures not exceeding 30°C.
Do not use after the date marked “EXP” on the pack.
Drugs should be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Not Applicable.

AVAILABILITY

* Tablets: Box of 30 tablets in PA/Al/PVDC blister pack of 15’s.

**LA Capsules: Box of 30 capsules in HDPE bottle.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

DDB Regulation requires prescription and dispensing through a Special Prescription Form for Dangerous Drugs by a current PDEA S2-licensed medical practitioner. It is a habit-forming drug.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Registration Number/Date of First Registration:

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Methylphenidate (Ritalin® LA)
20 mg Capsule: DR-XY43804/ 14 October 2014
30 mg Capsule: DR-XY43805/ 14 October 2014
40 mg Capsule: DR-XY43806/ 14 October 2014

Tablets: Manufactured by
Novartis Farmaceutica S.A.
Ronda de Santa Maria, 158 08210, Barberà del Vallès, Barcelona, Spain

LA Capsules: Manufactured by
Recro Gainesville LLC
1300 Gould Drive, Gainesville, GA 30504, USA

Imported by
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