Subject to the Swiss Federal Law on Narcotics and Psychotropic Substances.

NOVARTIS

Ritalin®/Ritalin®SR/ Ritalin® LA

Composition
Active substance:Methylphenidate hydrochloride

Excipients:
Ritalin tablet [10 mg]: calcium phosphate, lactose, wheat starch, gelatine, magnesium stearate, and talc.
Ritalin SR tablet [20 mg]: lactose, cetostearyl alcohol, magnesium stearate, hydroxypropyl methylcellulose, polyoxyl 40 hydrogenated castor oil, titanium dioxide (E 171), talc, carnauba wax, and fine black ink.
Ritalin LA capsule [10mg, 20 mg, 30 mg and 40 mg]: ammonio methacrylate copolymer, black iron oxide (E 172) (10 and 40 mg capsules only), gelatine, methacrylic acid copolymer, macrogol, red iron oxide (E 172) (10 and 40 mg capsules only), sugar spheres, talc, titanium dioxide (E 171), triethyl citrate, and yellow iron oxide (E 172) (10, 30 and 40 mg capsules only).

Pharmaceutical form and quantity of active substance per unit
Tablets (divisible) containing 10 mg methylphenidate hydrochloride.

SR (sustained-release) tablets (non-divisible) containing 20 mg methylphenidate hydrochloride.
LA (long-acting) modified-release capsules containing 10, 20, 30 or 40 mg methylphenidate hydrochloride for once-daily oral administration.

Indications/Potential uses
Ritalin/Ritalin SR/Ritalin LA is indicated as part of a comprehensive treatment strategy for attention deficit hyperactivity disorder (ADHD) in children aged 6 years and over and adolescents up to 18 years of age.
Treatment must be initiated and supervised by specialists in childhood/adolescent or adult behavioural disorders.
The efficacy of Ritalin/Ritalin SR/Ritalin LA in the treatment of ADHD was documented in controlled clinical trials in children and adolescents aged 6 to 17 years who met DSM-IV criteria for ADHD.
Use of Ritalin/Ritalin SR/Ritalin LA should be restricted to patients who require a drug whose effects last until evening following morning dosing.
Ritalin/Ritalin SR/Ritalin LA should be used as part of a comprehensive treatment programme when behavioural measures alone have proved insufficient. A comprehensive treatment program for ADHD may include psychological, educational and social measures.
The diagnosis should be made according to the DSM-IV criteria or ICD-10 classification, and should be based on a complete history and examination of the patient.

Special diagnostic considerations in children with hyperkinetic disorders
Treatment with Ritalin/Ritalin SR/Ritalin LA is not indicated in all children and adolescents with ADHD, and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms. Stimulants are not intended for use in patients with symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational measures are essential, and psychosocial intervention is often helpful.
The specific aetiology of this syndrome is unknown. Adequate diagnosis cannot be made with a single diagnostic test, but requires the use of medical, special psychological, educational and social resources. Learning may – but need not – be impaired.
Treatment with Ritalin/Ritalin SR/Ritalin LA may reduce the main symptoms of ADHD, including moderate to severe distractibility, short attention span, impulsivity, increased motor activity and abnormal social behaviour.
Narcolepsy
Symptoms include daytime sleepiness, inappropriate sleep episodes and sudden loss of voluntary muscle tone.

Dosage and Administration
Usual dosage
Ritalin/Ritalin SR/Ritalin LA dosage should be based on the individual patient's clinical needs and response.
Administration should be timed to coincide with periods of greatest educational, behavioural and social stress.
Ritalin/Ritalin SR/Ritalin LA should be started at a low dose, with increments at weekly intervals. Daily doses in excess of 60 mg are not recommended.

Ritalin tablets
Adults: The average daily dose is 20-30 mg, given in 2-3 divided doses. Some patients may require 40-60 mg daily, while for others 10-15 mg daily will be adequate.
Patients who have difficulty falling asleep if they take medication late in the day should take the last dose before 6 p.m. (18:00).

Children ≥6 years of age: Treatment is started with 5 mg (half a 10 mg tablet) once or twice daily (e.g. at breakfast and lunch), the daily dose subsequently being increased by 5-10 mg at weekly intervals. The total daily amount should be administered in divided doses.

Ritalin SR tablets
Adults and children (≥6 years of age): Ritalin SR tablets – while showing high pharmacokinetic variability – have a mean duration of action of about 8 hours. They can therefore be used in patients in whom a longer duration of action is required than that obtained with the standard tablets.
Dosage should be tailored to the individual patient's requirements. When switching patients from the standard to the SR tablets, the existing methylphenidate dose should be viewed only as a rough guide, since blood levels progress differently with the two forms and this may influence the efficacy of the preparation. In some cases it may be necessary to give a combination of standard and SR tablets in order to achieve a satisfactory effect.
Owing to individual variations in the duration of action of the SR tablets, administration in the middle of the day may sometimes be unavoidable.
Ritalin SR tablets must be swallowed whole, without crushing or chewing. They should be taken after meals, preferably after a substantial breakfast (see **Pharmacokinetics**). Ingestion with a high-fat meal may increase their absorption and duration of action.

Ritalin LA capsules for once-daily oral administration
Adults and children (≥6 years of age): Ritalin LA (long-acting methylphenidate hydrochloride capsules) is intended for once daily oral administration in the morning.
Overall exposure (AUC) of methylphenidate following a single-dose of Ritalin LA is comparable to that found with the same total dose of Ritalin administered twice daily.
The recommended dose of Ritalin LA for patients being switched from twice-daily Ritalin or Ritalin SR is shown below:

Previous Ritalin dose	Recommended Ritalin LA dose
5 mg Ritalin twice daily or 10 mg Ritalin twice daily or 20 mg Ritalin SR once daily	10 mg once daily or 20 mg once daily
15 mg Ritalin twice daily	30 mg once daily
20 mg Ritalin twice daily or 40 mg Ritalin SR once daily	40 mg once daily

For other methylphenidate regimens, the starting dose should be selected on the basis of the clinical situation. Ritalin LA dosage may be adjusted at weekly intervals in 10 mg increments.
Ritalin LA capsules may be taken with or without food. Ritalin LA capsules may be swallowed whole or opened and the contents sprinkled on food (see specific instructions below).
Ritalin LA capsules and/or their contents must not be crushed, chewed, or divided.

Administration by sprinkling capsule contents on food
The capsules may be carefully opened, and the contents sprinkled over a small amount of soft food (e.g. apple sauce). The food should not be warm because this might affect the modified-release properties of the formulation. The food-drug mixture should be consumed immediately in its entirety. It must not be set aside for later consumption.

Special dosage instructions
Children
Use of Ritalin/Ritalin SR/Ritalin LA in patients under 6 years of age has not been evaluated in controlled studies. Ritalin/Ritalin SR/Ritalin LA should not be used in patients under 6 years of age.

Note: The medicinal product should be withdrawn if symptoms do not improve within one month of a dose increase.
The dosage should be reduced or, if necessary, the medicinal product withdrawn, if symptoms worsen or adverse effects occur.
If the effect of the drug wears off too early in the evening, hyperactive behaviour and/or inability to fall asleep may recur. A small evening dose of Ritalin or an afternoon dose of Ritalin SR may help to solve this problem.
Ritalin/Ritalin SR/Ritalin LA should be withdrawn from time to time (at least once yearly) to reassess the benefit of treatment. Improvement in symptoms may even persist when the medicinal product is temporarily or permanently withdrawn. Drug treatment should not, and need not, be indefinite. It can usually be discontinued during or after puberty.

Pre-treatment screening
The patient's cardiovascular status, including blood pressure and heart rate, must be determined and documented prior to initiating treatment with Ritalin/Ritalin SR/Ritalin LA. As no long-term data are available, patients with a risk factor profile should undergo regular cardiovascular examination (see **Warnings and Precautions**).
Weight and height should also be measured before treatment and documented on a growth chart.
Before treatment with Ritalin is initiated, patients should be assessed for pre-existing cardiovascular and psychiatric disorders, and a family history should be taken focussing on any cases of sudden death, ventricular arrhythmia or psychiatric disorders.

Contraindications
– Known hypersensitivity to methylphenidate or any of the other ingredients of Ritalin/Ritalin SR/Ritalin LA indicated under **Composition**.
– Marked anxiety, tension or agitation, as Ritalin/Ritalin SR/Ritalin LA may aggravate these symptoms.
– Hyperthyroidism.
– Arrhythmias.
– Pre-existing cardiovascular disorders including severe hypertension, angina pectoris, cardiac insufficiency, heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
– Glaucoma.
– Phaeochromocytoma.
– Diagnosis or family history of Tourette's syndrome.
– Treatment with monoamine oxidase (MAO) inhibitors and for at least 14 days after withdrawal of a MAO inhibitor (during which acute hypertension may occur; see **Interactions**).
– Diagnosis or history of severe depression, anorexia nervosa, psychotic symptoms, suicidal tendency, mania, schizophrenia or borderline personality disorder, because the medicinal product could exacerbate these conditions.
– Arterial occlusive diseases.
– Pre-existing cerebrovascular disorders such as cerebral aneurysm, vascular abnormalities including vasculitis or stroke.
– Misuse of alcohol and drugs.

Warnings and Precautions
Sudden death has been reported in children with cardiac structural abnormalities in the heart who were treated with stimulants, including methylphenidate. Methylphenidate should therefore not be used in children with structural cardiac abnormalities or prior cardiovascular disease.
Patients considered for treatment with Ritalin/Ritalin SR/Ritalin LA should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical examination performed to identify any existing cardiac disease, and should undergo further cardiological investigations (e.g. electrocardiogram, echocardiogram) if preliminary findings suggest such disease.
Cardiovascular status should be monitored. Blood pressure and heart rate should be checked and documented at every dose adjustment or at appropriate intervals (but at least every 6 months), and thereafter if ever clinically indicated.
Children who develop symptoms such as palpitations, exertional chest pain, syncope or other symptoms suggestive of cardiac disease during treatment with Ritalin/Ritalin SR/Ritalin LA should undergo prompt cardiological evaluation.
Central nervous system (CNS) stimulants including methylphenidate have been associated with the onset or exacerbation of motor and verbal tics. Patients should therefore undergo a clinical evaluation for tics, including family history, before treatment with stimulants.
Growth retardation (reduced weight and/or height gain) has been reported in children receiving long-term treatment with Ritalin/Ritalin SR/Ritalin LA. Follow-up studies in children aged 7 to 10 years suggest that children constantly medicated with methylphenidate (e.g. 7 days a week for 1 year) may show temporary slowing in growth rate (on average 2 cm less longitudinal growth and 2.7 kg less weight gain over 3 years). Patients who require long-term treatment should therefore be carefully monitored (at least every 6 months) for height, weight and appetite, and documented in a growth chart. Treatment should be interrupted in patients who are not growing or gaining weight as expected.
There is clinical evidence that psychiatric disorders (including addictive and suicidal behaviour) and weight and appetite loss occur more frequently during administration of medicinal products containing the active substance methylphenidate. Careful screening for such changes, or for signs of medication misuse and abuse, must be undertaken at each visit and each dose adjustment.
Ritalin/Ritalin SR/Ritalin LA should not be used for the prevention or treatment of normal fatigue states.
Attention should be paid to the emergence or worsening of aggressive behaviour in patients starting treatment with methylphenidate. Close monitoring is required. Aggression is often associated with ADHD; however, unexpected emergence or worsening of aggression has been reported during treatment with methylphenidate. Interruption of treatment may be considered (see **Adverse effects**).
Close supervision is required if the medicinal product is withdrawn, since this may precipitate withdrawal symptoms and unmask depression or effects of chronic hyperactivity. Some patients may therefore require long-term follow-up.
For interactions with centrally acting alpha-2 agonists such as clonidine, see **Interactions**.
Symptoms of visual disturbances have occurred in rare cases, with reports of accommodation difficulties and blurred vision.
Insufficient data are available on efficacy, safety and dosage in children under 6 years of age.

Interactions
Pharmacodynamic interactions
Halogenated anaesthetics: There is a risk of a sudden increase in blood pressure during surgery. If surgery is planned, methylphenidate should not be taken on the day of surgery.
Antihypertensives: Ritalin may reduce the blood pressure-lowering effect of antihypertensives.
Concomitant use with drugs that elevate blood pressure:
Because of the possible increase in blood pressure, Ritalin/Ritalin SR/Ritalin LA should be used with caution in combination with vasopressor agents (see **Warnings and Precautions**). Ritalin is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, reversible and irreversible MAO inhibitors due to the risk of a hypertensive crisis (see **Contraindications**).
Concomitant use with centrally acting alpha-2 agonists (e.g. clonidine):
There have been reports of serious adverse effects, including sudden death, during concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine, or other centrally acting alpha-2 agonists, has not yet been systematically evaluated.
Concomitant use with dopaminergic medicinal products:
As a dopamine reuptake inhibitor, Ritalin may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) and dopamine antagonists (antipsychotics such as haloperidol). Coadministration of Ritalin with antipsychotics is not recommended because of their opposed mechanisms of action.
Concomitant use with alcohol:
Alcohol may exacerbate the adverse CNS effects of psychotropic drugs, including Ritalin/Ritalin SR/Ritalin LA. It is therefore advisable for patients 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. For their part, the d- and l- enantiomers of methylphenidate do not inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.
Coadministration of Ritalin does not increase plasma concentrations of the CYP2D6 substrate desipramine.
Case reports suggest a potential interaction of Ritalin with coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic antidepressants, but pharmacokinetic interactions were not confirmed when explored at higher sample sizes. The dosage of these drugs may have to be reduced when they are coadministered with Ritalin.
An interaction with the anticoagulant ethyl biscoumacetate in 4 patients was not confirmed with a higher sample size (n = 12).

Pregnancy and Lactation
Pregnancy
Clinical studies on the safety of methylphenidate in pregnant women have not been carried out.
In animal studies, methylphenidate is considered to be possibly teratogenic in rabbits (see **Preclinical data**).
Ritalin/Ritalin SR/Ritalin LA must not be given to pregnant women unless absolutely necessary.

Lactation
Case reports showed that methylphenidate passed into breast milk, reaching a milk-to-plasma ratio of approximately 2.5 (see **Pharmacokinetics**).
A decision should be made whether to abstain from breast-feeding or to abstain from Ritalin therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

Effects on ability to drive and use machines
Ritalin may cause drowsiness, blurred vision, hallucinations or other CNS side effects (see **Adverse effects**). Patients experiencing such side effects should refrain from driving, using machines or engaging in other potentially dangerous activities.

Adverse effects
Frequencies (defined): Very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10 000 to <1/1000), very rare (<1/10 000).
Adverse drug reactions have been observed during use of medicinal products containing methylphenidate, and should be interpreted as class effects.
The most frequently observed of these adverse effects are:

Infections: Nasopharyngitis.
Metabolism and nutrition disorders: Anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children.

Psychiatric disorders: Insomnia, nervousness, anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour.

Nervous system disorders: Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence.

Cardiac disorders: Arrhythmia, tachycardia, palpitations.

Vascular disorders: Hypertension.

Respiratory and thoracic disorders: Cough, pharyngolaryngeal pain.

Gastrointestinal disorders: Abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting, dry mouth.

Skin disorders: Alopecia, pruritus, rash, urticaria.

Musculoskeletal disorders: Arthralgia.

General disorders: Pyrexia, growth retardation during prolonged use in children.

Investigations: Changes in blood pressure and heart rate (usually an increase), weight loss.
Attention must also be drawn to the following clinically important or *serious* adverse effects of methylphenidate-containing medicinal products, regardless of their frequency:

Psychiatric disorders: Suicide, attempted suicide, suicidal ideation, stereotypical (pathologically repetitive) behaviours, tactile hallucinations.

Nervous system disorders: Choreoathetoid movements, tics or exacerbation of existing tics, reversible neurological deficits, migraine, neuroleptic malignant syndrome.

Eye disorders: Accommodation difficulties.

Cardiac disorders: Sudden cardiac death, myocardial infarction.

Vascular disorders: Cerebrovascular disorders or haemorrhage, vasculitis, Raynaud's phenomenon, peripheral coldness (cold hands or feet).

Gastrointestinal disorders: Hepatic impairment.

Skin disorders: Exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, fixed drug eruption.

Renal and urinary disorders: Haematuria.

Reproductive system and breast disorders: Gynaecomastia.
Adverse drug reactions have also been reported in association with use of Ritalin:

Metabolism and nutrition disorders
Common: Decreased appetite.
Uncommon: Anorexia, moderately reduced weight and height gain in children undergoing long-term treatment.

Blood and lymphatic system disorders
Very rare: Leukopenia, thrombocytopenia and anaemia.
Immune system disorders
Very rare: Hypersensitivity reactions, including angioedema and anaphylaxis.

Psychiatric disorders
Very common: Insomnia, nervousness.
Common: Abnormal behaviour, aggression, agitation, anxiety, depression, irritability.
Very rare: Hyperactivity, visual and tactile hallucinations, transient depressed mood (sadness, anxiety, tearfulness), psychotic disorders, tics or exacerbation of pre-existing tics.
There have been known cases of suicidal behaviour (including completed suicide) in patients treated with methylphenidate. However, the role of methylphenidate in these cases is unclear.

Nervous system disorders
Very common: Nervousness and insomnia. These occur at the start of treatment but can usually be controlled by reducing the dosage and/or omitting the afternoon or evening dose.
Common: Headache, drowsiness, dizziness, dyskinesia.
Very rare: Convulsions, choreoathetosis, tics – or exacerbation of existing tics – and Tourette's syndrome, transient depressed mood, cerebral arteritis and/or occlusion, cerebrovascular disorders, cerebral haemorrhages and cerebrovascular accidents. There have been very rare and poorly documented reports of neuroleptic malignant syndrome (NMS), most of which involved patients who were also receiving other medications. The role played by Ritalin in these cases is unclear.

Eye disorders
Rare: Accommodation disorders and blurred vision.

Cardiac disorders
Common: Tachycardia, palpitations, arrhythmias, changes in blood pressure and heart rate (usually an increase).
Rare: Angina pectoris.
Very rare: Cardiac arrest.

Vascular disorders
Very rare: Cerebrovascular disorders, vasculitis.

Gastrointestinal disorders
Common: Abdominal pain, nausea, stomach discomfort and vomiting. These usually occur at the start of treatment and may be alleviated by concomitant food intake. Dry mouth. Decreased appetite (usually transient, however).
Very rare: Diarrhoea, constipation.

Hepatobiliary disorders
Very rare: Hepatic dysfunction, ranging from transaminase elevation to hepatic coma.

Skin disorders
Common: Rash, exanthema, pruritus, urticaria, fever, scalp hair loss.
Very rare: Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme, angioedema, inflammation of the oral mucosa (in adults with narcolepsy).

Musculoskeletal disorders
Common: Arthralgia.
Very rare: Muscle cramps.

General disorders
Common: Fever.
Rare: Moderately reduced weight gain and slight growth retardation with long-term use in children.

Overdose
Signs and symptoms
Signs and symptoms of Ritalin/Ritalin SR/Ritalin LA overdosage, which are mainly due to CNS overstimulation and exaggerated sympathomimetic effects, include: vomiting, agitation, tremor, hyperreflexia, muscle twitching, convulsions (possibly followed by coma), disorientation, euphoria, confusion, hallucinations (acoustic and/or visual), delirium, sweating, flushing, headache, pyrexia, tachycardia, palpitations, increased heart rate, sinus arrhythmia, hypertension, mydriasis and mucosal dryness.

Management
When treating overdose, it should be borne in mind that with Ritalin LA (methylphenidate hydrochloride modified-release capsules) a second release of methylphenidate occurs approx. 4-6 hours after administration of the capsule.
Management consists in providing supportive measures and symptomatic treatment of life-threatening events (e.g. hypertensive crisis, cardiac arrhythmias, convulsions).
Supportive measures should protect patients from self-injury and from external stimuli that could exacerbate the overstimulation already present.
If the patient is conscious, the stomach may be emptied by inducing vomiting, with subsequent administration of activated charcoal. Gastric lavage is necessary in hyperactive or unconscious patients, or in patients with reduced respiratory function.
Intensive care must be provided to maintain adequate circulation and respiration. External cooling procedures may be required to reduce hyperpyrexia.
The efficacy of peritoneal dialysis or extracorporeal haemodialysis for Ritalin/Ritalin SR/Ritalin LA overdosage has not been established.

Properties and Actions
ATC code: N06BA04

Mechanism of action
Methylphenidate is a CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in humans is not yet fully elucidated, but its stimulant effects are thought to be due to inhibition of dopamine reuptake in the striatum without triggering the release of dopamine. The mechanism by which methylphenidate exerts its mental and behavioural 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. Ritalin is a racemate consisting of a 1:1 mixture of d-methylphenidate (d-MPH) and l-methylphenidate (l-MPH). The l-enantiomer is thought to be pharmacologically inactive.

Pharmacokinetics
Absorption
Tablets
After oral administration, methylphenidate hydrochloride (the active substance of Ritalin tablets) is rapidly and almost completely absorbed. Owing to extensive first-pass metabolism, the absolute bioavailability is 22 ± 8% for the d-enantiomer and 5 ± 3% for the l-enantiomer. Ingestion with food has no relevant effect on absorption.
On average, peak plasma concentrations of about 40 nmol/litre (11 ng/ml) are reached 2 hours after administration. There are considerable inter- and intra-individual variations in peak plasma concentrations. The area under the plasma concentration curve (AUC) and the peak plasma concentration (C_{max}) are proportional to the size of the dose. There is no correlation between peak plasma concentration and pharmacological effect.
SR tablets
In the fasting state, absorption is about 37% slower than from the standard tablets, resulting in less fluctuation in the plasma concentration. C_{max} is 40% lower and is attained later (after 3 hours), although the AUC is the same.
Following a high-fat meal both the AUC and C_{max} are significantly raised (25% and 27%, respectively), while the rate of absorption (C_{max}/AUC) remains constant. The time to peak plasma level (t_{max}) is slightly reduced (mean t_{max}: 2.5 hours).
LA capsules
Following oral administration of Ritalin LA (methylphenidate hydrochloride modified-release capsules for once-daily oral administration) to children diagnosed with ADHD and to adults, methylphenidate is rapidly absorbed and produces a bi-modal plasma concentration curve (i.e. two distinct peaks approx. four hours apart). In children and adults the relative bioavailability of Ritalin LA given once daily is comparable to the same total dose of Ritalin or methylphenidate tablets given twice daily.
The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for Ritalin LA given once daily than for Ritalin tablets given twice daily.

Effect of concomitant food intake: Ritalin LA may be taken with or without food. There were no relevant differences in the bioavailability of Ritalin LA when administered with either a high-fat breakfast or apple sauce, as compared with administration in the fasting state. There is no evidence of a fall in concentration due to concomitant food intake.
For patients unable to swallow the capsule, the contents may be sprinkled on soft food such as apple sauce (see **Dosage and Administration**).

Distribution
In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Binding to plasma proteins is low (10-33%). The volume of distribution is 2.65 ± 1.11 litres/kg for d-MPH and 1.80 ± 0.91 litres/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 effects were not noted in either infant (6 and 11 months old).

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

Elimination
Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The systemic clearance is 0.40 ± 0.12 litres/hour/kg for d-MPH and 0.73 ± 0.28 litres/hour/kg for l-MPH. Within 48-96 hours of oral administration, 78-97% of the dose is excreted in the urine, and 1-3% in the faeces, in the form of metabolites. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose (60-86%) is excreted in the urine as alpha-phenyl-2-piperidine acetic acid.
There is no significant difference in the elimination half-life or cumulative renal elimination of alpha-phenyl-2-piperidine acetic acid following administration of the sustained-release tablets.

Pharmacokinetics in special patient populations
Hyperactive children
There are no differences in the pharmacokinetics of methylphenidate between hyperactive children and healthy adult volunteers.

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

Preclinical data
Reproductive toxicity
Methylphenidate is considered to be possibly teratogenic in rabbits. In a reproductive toxicity study with methylphenidate in rabbits, spina bifida and malrotated hind limbs were 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 maximum recommended human dose (MRHD) of 60 mg. Exposure at the next lower dose, for which no spina bifida was found, was 0.7 times the extrapolated exposure at the MRHD. A second study was conducted with a high dose of 300 mg/kg/day, which was considered to be maternally toxic. However, no spina bifida was observed in twelve surviving litters (92 fetuses). Exposure (AUC) at 300 mg/kg was 7.5 times the extrapolated exposure at the MRHD.
Methylphenidate was not shown to be teratogenic in animal studies in rats. A high daily dose of 75 mg/kg (20.9 times higher than the exposure [AUC] at the MRHD) resulted in the development of fetal toxicity, involving an increased incidence of fetuses with delayed ossification of the skull and hyoid bone and fetuses with short supernumerary ribs.

Carcinogenicity
In a lifetime study in mice, methylphenidate at doses of approx. 60 mg/kg/day (approx. 35 times the MRHD) caused an increased frequency of hepatocellular adenomas (benign hepatic tumours) and, in males only, an increase in hepatoblastomas (malignant hepatic tumours). No overall increase was seen in the frequency of malignant hepatic tumours. The mouse strain used is particularly prone to the development of hepatic tumours and the significance of these findings for humans is not known.
Similar studies in rats showed no evidence of carcinogenicity.

Mutagenicity
Sister chromatid exchange and chromosome aberrations were elevated in one *in vitro* study in Chinese hamster ovary (CHO) cells. However, no genotoxic effects were seen in several other *in vitro* assays, including the following three: Ames reverse mutation test, mouse lymphoma forward mutation test, human lymphocyte chromosome aberration test. Two *in vivo* mouse bone marrow micronucleus tests yielded no evidence of clastogenic or aneugenic effects at doses up to 250 mg/kg. B6C3F1 mice from the same strain that showed liver tumours 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 Big Blue mice, micronuclei in peripheral blood reticulocytes, HPRT mutations and chromosomal aberrations in rhesus monkeys and pig A locus mutations in adolescent rats.

Adolescent behavioural development
Repeated oral administration of methylphenidate in young rats resulted in a reduction in locomotor activity at doses of 50 mg/kg/day (29 times higher than the MRHD) that was attributable to the excessive pharmacokinetic activity of methylphenidate. In addition, in female rats a deficit in the acquisition of specific learning skills was observed at the highest dose of 100 mg/kg/day (58 times higher than the MRHD). The clinical relevance of these findings is not known.

Other information
Effect on diagnostic tests
Methylphenidate may induce false positive results in laboratory tests for amphetamines, in particular those using immunoassay screen tests.

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Ritalin tablets: Protect from moisture and do not store above 30°C.
Ritalin SR tablets: Protect from moisture and do not store above 30°C.
Ritalin LA capsules: Keep tightly sealed in the original container, and do not store above 30°C.
Keep out of the reach of children.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box.

Information last revised
February 2013

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists