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Drug Regulatory Affairs

**RITALIN<sup>®</sup> / RITALIN<sup>®</sup> SR / RITALIN<sup>®</sup> LA**  
**(methylphenidate hydrochloride)**

Ritalin 10 mg / Ritalin SR 20 mg / Ritalin LA 10mg, 20 mg, 30 mg, 40 mg

**Core Data Sheet**

**Version 1.0**

**NOTICE**

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosing, pharmacovigilance and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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**Table of contents**

1	Trade name(s).....	3
2	Description and Composition.....	3
3	Indications .....	4
4	Dosage and Administration .....	4
5	Contraindications.....	6
6	Warnings and Precautions .....	7
7	Adverse drug reactions .....	10
8	Interactions .....	12
9	Pregnancy and Breast-feeding.....	13
10	Overdosage .....	14
11	Clinical pharmacology.....	14
12	Clinical studies .....	17
13	Non-clinical safety data.....	18
14	Pharmaceutical information.....	19
15	References .....	<b>Error! Bookmark not defined.</b>

## 1 Trade name(s)

RITALIN<sup>®</sup> 10 mg Tablets.

RITALIN<sup>®</sup> SR 20 mg Tablets.

RITALIN<sup>®</sup> LA 10 mg, 20 mg, 30 mg or 40 mg Capsules.

## 2 Description and Composition

### Pharmaceutical form(s)

Ritalin: Immediate-release tablet, divisible.

Ritalin SR: Sustained-release tablet, non-divisible.

Ritalin LA: Modified-release capsule, hard [95].

### Active substance(s)

The active substance is methylphenidate hydrochloride.

Ritalin tablet contains 10 mg methylphenidate hydrochloride.

Ritalin SR tablet contains 20 mg methylphenidate hydrochloride.

Ritalin LA capsule contains 10 mg, 20 mg, 30 mg and 40 mg methylphenidate hydrochloride [141,94].

### Active moiety

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

### 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) [141,94].

### 3 Indications

#### Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV) [69]

ADHD was previously known as attention-deficit disorder or minimal brain dysfunction. Other terms used to describe this behavioural syndrome include: hyperkinetic disorder [70], minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children [13]. Ritalin is indicated as part of a comprehensive treatment programme which typically includes psychological, educational, and social measures and is aimed at stabilising children with a behavioural syndrome characterised by moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity [14-19,69,70]. The diagnosis should be made according to DSM-IV criteria [69] or the guidelines in ICD-10 [70]. Non-localising (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 [20].

#### Special Diagnostic Considerations for ADHD

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Proper diagnosis requires medical and neuropsychological, educational, and social investigation [21-23]. Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity, minor neurological signs, and abnormal EEG [24-26,52]. 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 [52]. 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 [13,52]. 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 [52].

#### Narcolepsy (Ritalin and Ritalin SR only)

Symptoms include daytime sleepiness, inappropriate sleep episodes, and sudden loss of voluntary muscle tone [27-29,71].

### 4 Dosage and Administration

#### General

The dosage of Ritalin should be individualised 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, behavioural, and social stress.

Ritalin should be started at a low dose, with increments at weekly intervals. Daily doses above 60 mg are not recommended.

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 behaviour and/or inability to go to sleep may recur [52]. A small evening dose of the normal tablet or an afternoon dose of the SR tablet may help to solve this problem. Ritalin should be discontinued periodically to assess the child's condition. Improvement may continue when the drug is temporarily or permanently discontinued.

Drug treatment should not, and need not, be indefinite. It can usually be discontinued during or after puberty. [69,70,72-80,144].

### **Pre-treatment screening**

Before initiating Ritalin treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular arrhythmia and psychiatric disorders (see sections 5 Contraindications and 6 Warnings and precautions) [144].

### **Children (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 [5,51]. The total daily dosage should be administered in divided doses.

**SR Tablets:** Ritalin SR tablets have a duration of action of about 8 hours. They may therefore be used when a prolonged effect is desired exceeding the duration of action of standard Ritalin tablets. Ritalin SR tablets must be swallowed whole and never crushed or chewed and should be taken after meals, preferably after a substantial breakfast (see section 11 Clinical pharmacology).

**LA Capsules:** Ritalin LA (methylphenidate hydrochloride modified-release capsules) is for oral administration once daily in the morning. The recommended starting dose of Ritalin LA is 20 mg [96,97]. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with Ritalin LA 10 mg [97].

Ritalin LA capsules may be administered with or without food. They may be swallowed as whole capsules or alternatively may be administered by sprinkling the contents over a small amount of food (see specific instructions below) [98].

Ritalin LA capsules and/or their contents should not be crushed, chewed, or divided [98].

### Ritalin LA administration by sprinkling capsule contents on food

The capsules may be carefully opened and the beads sprinkled over soft food (e.g. apple-sauce) [98]. The food should not be warm because this could affect the modified-release properties of this formulation [99]. 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.

Ritalin LA, administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of Ritalin administered twice daily. [96,100].

### Switching patients to Ritalin LA

The recommended dose of Ritalin LA in patients being switched from the immediate-release formulation or the sustained-release formulation is provided below [96,97,100].

**Table 4-1 Recommended daily dose when switching patients to Ritalin LA**

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

For other methylphenidate regimens, clinical judgement should be used when selecting the starting dose. Ritalin LA dosage may be adjusted at weekly intervals in 10 mg increments [97].

### Adults

**Tablets:** The average daily dose is 20 to 30 mg, given in 2 to 3 divided doses [5].

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.

**SR Tablets:** Ritalin SR tablets have a duration of action of about 8 hours. They may therefore be used when a prolonged effect is desired exceeding the duration of action of standard Ritalin tablets. Ritalin SR tablets must be swallowed whole and never crushed or chewed and should be taken after meals, preferably after a substantial breakfast (see section 11 Clinical pharmacology).

## 5 Contraindications

- Hypersensitivity to methylphenidate or to any of the excipients [81].

- Anxiety, tension [21,54,59].
- Agitation [21,54,59].
- Hyperthyroidism [21,54,59].
- Pre-existing cardiovascular disorders including severe hypertension, angina, arterial occlusive disease; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels) [144].
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 2 weeks of discontinuing those drugs, due to risk of hypertensive crisis (see section 8 Interactions) [144]
- Glaucoma [21,54,59].
- Pheochromocytoma [118].
- Diagnosis or family history of Tourette's syndrome [21,30,31].

## 6 Warnings and Precautions

### General

Treatment with Ritalin 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 Ritalin should depend on an assessment of the severity of symptoms and their appropriateness to the child's age, and not simply 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.

### 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 children 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 Ritalin, generally should not be used in patients with known structural cardiac abnormalities [117] or other serious cardiac disorders that may increase the risk of sudden death due to sympathomimetic effects of a stimulant drug. Before initiating Ritalin treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see section 4 Dosage and administration) [144].

**Cardiovascular Conditions:** Ritalin is contraindicated in patients with severe hypertension [117]. Ritalin 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

[117,144]. Severe cardiovascular disorders are contraindicated (see section 5 Contraindications).

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

**Misuse and Cardiovascular Events:** Misuse of stimulants of the central nervous system, including Ritalin, may be associated with sudden death and other serious cardiovascular adverse events [117].

### **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 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, paragraph on Cardiovascular Conditions and section 8 Interactions) [119].

### **Psychiatric [120,144]**

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with Ritalin, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section 4 Dosage and administration).

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 or mania have been reported in patients administered usual prescribed doses of stimulant products, including Ritalin (see section 7 Adverse drug reactions). Physicians should consider treatment discontinuation.

**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.

**Tics:** Ritalin is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see section 7 Adverse drug reactions). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate for ADHD treatment. Patients should be regularly monitored for the emergence or worsening of tics during treatment with Ritalin [144].

#### **Growth retardation**

Moderately reduced weight gain and slight growth retardation have been reported with the long-term use of stimulants, including Ritalin, in children (see section 7 Adverse drug reactions) [41]. Growth should be monitored as clinically necessary during treatment with Ritalin, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted [144].

#### **Seizures**

Ritalin 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 [67,68]. If seizure frequency increases, Ritalin should be discontinued.

#### **Abuse**

Chronic abuse of Ritalin can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially with parenteral abuse [47,48]. Clinical data indicate that children given Ritalin are not more likely to abuse drugs as adolescents or adults [45,46,52].

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 [47,48]. Some patients may require long-term follow-up.

#### **Haematological effects**

The long-term safety and efficacy profiles of Ritalin 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 haematological disorders appropriate medical intervention should be considered (see section 7 Adverse drug reactions) [60,144].

**Use in children under 6 years of age**

Ritalin 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**

Ritalin may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see section 7 Adverse drug reactions). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

**7 Adverse drug reactions**

Nervousness and insomnia are very common adverse reactions which occur at the beginning of Ritalin treatment but can usually be controlled by reducing the dosage and/or omitting the afternoon or evening dose [21,32,33,38].

Decreased appetite is also common but usually transient [33,38]. Abdominal pain, nausea and vomiting are common, usually occur at the beginning of treatment and may be alleviated by concomitant food intake [32,38,55].

Adverse reactions listed in Table 7-1 are ranked under headings of frequency, using the following convention: very common ≥ 10%, common ≥ 1% to < 10%; uncommon ≥ 0.1% to < 1%; rare ≥ 0.01% to < 0.1%; very rare < 0.01%.

**Table 7-1 Adverse reactions reported with Ritalin use**

<b>Blood and the lymphatic system disorders</b>	
Very rare:	Leucopenia, thrombocytopenia, anaemia [60].
<b>Immune system disorders</b>	
Very rare:	Hypersensitivity reactions [116].
<b>Metabolism and nutrition disorders</b>	
Common:	Decreased appetite
Rare:	Moderately reduced weight gain during prolonged use in children [33,41-43].
<b>Psychiatric disorders</b>	
Very common:	Nervousness, insomnia
Very rare:	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations) [120], transient depressed mood [34-38,53,103].
<b>Nervous system disorders</b>	
Common:	Headache, drowsiness, dizziness, dyskinesia [29,40].
Very rare:	Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome [35],

**Comment:** Add 59 and 60 ?

	cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents [34,38,58,119].
<b>Eye disorders</b>	
Rare:	Difficulties in visual accommodation, blurred vision [65].
<b>Cardiac disorders</b>	
Common:	Tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase) [29,39,59].
Rare:	Angina pectoris [59,60].
<b>Gastrointestinal disorders</b>	
Common:	Abdominal pain, nausea, vomiting, dry mouth [29,32,38].
<b>Hepatobiliary disorders</b>	
Very rare:	Abnormal liver function, ranging from transaminase elevation to hepatic coma [83].
<b>Skin and subcutaneous tissue disorders</b>	
Common:	Rash, pruritus, urticaria, fever, scalp hair loss [29,36,40].
Very rare:	Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme [60].
<b>Musculoskeletal and connective tissue disorders</b>	
Common:	Arthralgia [29,40].
Very rare:	Muscle cramps [34,38].
<b>General disorders and administration site conditions</b>	
Rare:	Slight growth retardation during prolonged use in children [33,41-43].

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 [82].

### **Additional adverse reactions reported with other methylphenidate-containing products**

The list below shows adverse reactions not listed for Ritalin (see Table 7-1) that have been reported with other methylphenidate-containing products based on clinical trials data and post-market spontaneous reports [144].

**Infections and infestations:** Nasopharyngitis

**Blood and lymphatic disorders:** Pancytopenia

**Immune system disorders:** Hypersensitivity reactions such as auricular swelling

**Psychiatric disorders:** Anxiety, irritability, aggression, affect lability, agitation, abnormal behaviour or thinking, anger, suicidal ideation or attempt (including completed suicide), mood altered, mood swings, hypervigilance, mania, disorientation, libido disorder, apathy, repetitive

behaviours, over-focussing, confusional state, dependence, cases of abuse and dependence have been described, more often with immediate release formulations.

**Nervous system disorders:** Tremor, reversible ischaemic neurological deficit, migraine

**Eye disorders:** Diplopia, Mydriasis, visual disturbance

**Cardiac disorders:** Cardiac arrest, myocardial infarction

**Vascular disorders:** Peripheral coldness, Raynaud's phenomenon

**Respiratory, thoracic and mediastinal disorders:** Cough, pharyngolaryngeal pain, dyspnoea

**Gastrointestinal disorders:** Diarrhoea, constipation

**Skin and subcutaneous tissue disorders:** Angioneurotic oedema, hyperhidrosis, erythema, fixed drug eruption

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

**Renal and urinary disorders:** Haematuria

**Reproductive system and breast disorders:** Gynaecomastia

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

**Investigations:** Weight decreased, cardiac murmur

## 8 Interactions

### Pharmacodynamic interactions

#### Anti-hypertensive drugs

Ritalin may decrease the effectiveness of drugs used to treat hypertension [121].

#### Use with drugs that elevate blood pressure

Ritalin should be used with caution in patients being treated with drugs that elevate blood pressure [63] (see also paragraph on Cerebrovascular Conditions in section 6 Warnings and precautions).

Because of possible hypertensive crisis, Ritalin is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 5 Contraindications) [144].

#### Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including Ritalin [59,66,145]. It is therefore advisable for patients to abstain from alcohol during treatment.

#### Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, Ritalin should not be taken on the day of surgery [144].

**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. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated [144].

**Use with dopaminergic drugs**

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 [121].

**Pharmacokinetic interactions [121]**

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.

Case reports suggested a potential interaction of Ritalin with coumarin anticoagulants, some anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic antidepressants [50] but pharmacokinetic interactions were not confirmed when explored at higher sample sizes [121]. 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 higher sample size (n=12) [121].

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

**Drug/Laboratory test**

Methylphenidate may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test [104].

## 9 Pregnancy and Breast-feeding

**Pregnancy**

Studies to establish safe use of methylphenidate in pregnant women have not been conducted. Ritalin should not be given to pregnant women unless the potential benefit outweighs the risk to the foetus (see section 13 Non-clinical safety data).

**Breast-feeding**

It is not known whether the active substance of Ritalin and/or its metabolites pass into breast milk, but for safety reasons, breast-feeding mothers should not use Ritalin.

## 10 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, and dryness of mucous membranes [59].

### Management

When treating overdose, practitioners should bear in mind that a second release of methylphenidate from Ritalin LA (methylphenidate hydrochloride modified-release capsules) occurs at approximately four hours after administration [96,98,100].

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 [105,106].

The efficacy of peritoneal dialysis or extracorporeal haemodialysis for Ritalin 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 hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an infusion of calcium gluconate [3,8,42].

## 11 Clinical pharmacology

Pharmacotherapeutic group: psychostimulants - ATC code: NO6B AO4.

### Pharmacodynamic properties

Ritalin is a racemate consisting of a 1:1 mixture of d-methylphenidate (d-MPH) and l-methylphenidate (l-MPH) [107].

Ritalin is a mild CNS stimulant with more prominent effects on mental than on motor activities [84]. Its mode of action in man is not completely understood, but its stimulant effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine [1,84,121].

The mechanism by which Ritalin 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.

The l-enantiomer is thought to be pharmacologically inactive [121].

The effect of treatment with 40 mg dexamethylphenidate hydrochloride, the pharmacologically active d-enantiomer of Ritalin, 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 [146].

## Pharmacokinetic properties

### Absorption

#### Tablets

After oral administration the active substance (methylphenidate hydrochloride) is rapidly and almost completely absorbed [9]. Owing to extensive first-pass metabolism, the absolute bioavailability was  $22 \pm 8$  % for the d-enantiomer and  $5 \pm 3$  % for the l-enantiomer [121]. Ingestion with food has no relevant effect on absorption [121]. Peak plasma concentrations of about 40 nmol/L (11 ng/mL) are reached on average 1 to 2 hours after administration [121]. Peak plasma concentrations vary markedly between patients [7]. The area under the concentration-time curve (AUC), and the peak plasma concentration ( $C_{\max}$ ) are proportional to the dose [2,8].

#### SR Tablets

In the fasted state, absorption of methylphenidate from Ritalin 20 mg SR tablets is 37 % slower than with the standard tablets and results in smaller fluctuations of the plasma concentration.  $C_{\max}$  is lower (by 40 %) and is attained later (at 3 hours) but the total amount absorbed (AUC) is the same [85,86]. After a high-fat meal, both AUC (by 25 %) and  $C_{\max}$  (by 27 %) are significantly higher, although the rate of absorption ( $C_{\max}/\text{AUC}$  ratio) remains the same. Time to  $C_{\max}$  ( $T_{\max}$ ) is also slightly faster after a high-fat meal (median  $T_{\max}$ : 2.5 hours) as compared to without food (median  $T_{\max}$ : 3 hours).

#### LA Capsules

Following oral administration of Ritalin LA (modified-release capsules) to children diagnosed with ADHD [96] and adults [98,100], methylphenidate is rapidly absorbed and produces a bimodal plasma concentration-time profile (i.e. two distinct peaks approximately four hours apart). The relative bioavailability of Ritalin LA given once daily is comparable to the same total dose of Ritalin or methylphenidate tablets given twice a day in children and in adults [96,100,101].

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for Ritalin LA given once a day compared to Ritalin tablets given twice a day [96,100].

### Food Effects

Ritalin LA may be administered with or without food. There were no differences in the bioavailability of Ritalin LA 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 [98].

For patients unable to swallow the capsule, the contents may be sprinkled on soft food such as apple-sauce and administered (see section 4 Dosage and administration) [98].

### Distribution

In blood, methylphenidate and its metabolites are distributed between plasma (57 %) and erythrocytes (43 %) [9]. Binding to plasma proteins is low (10 to 33 %) [3,10]. The volume of distribution was  $2.65 \pm 1.11$  L/kg for d-MPH and  $1.80 \pm 0.91$  L/kg for l-MPH [121].

### Biotransformation

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 [2,3]. The 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 [2,5]. 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 [10,61,62].

### Elimination

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The systemic clearance is  $0.40 \pm 0.12$  L/h/kg for d-MPH and  $0.73 \pm 0.28$  L/h/kg for l-MPH [121]. After oral administration, 78 to 97 % of the dose is excreted in the urine and 1 to 3 % in the faeces in the form of metabolites within 48 to 96 hours [2]. Only small quantities (< 1 %) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as alpha-phenyl-2-piperidine acetic acid (60 to 86 %) [3,4,9].

The elimination half-life and the cumulative urinary excretion of alpha-phenyl-2-piperidine acetic acid are not significantly different for SR tablets.

### Characteristics in patients

There are no apparent differences in the pharmacokinetics of methylphenidate between hyperactive children and healthy adult volunteers [2,6,7]. 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 [2]. However, renal excretion of the metabolite alpha-phenyl-2-piperidine acetic acid may be reduced [2].



## 12 Clinical studies

Ritalin has been used for over 40 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 [152-156].

Studies in the published literature have shown Ritalin to significantly improve daytime sleepiness and cataplexy [157-162].

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 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 [97].

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. The CADS-T assesses symptoms of hyperactivity and inattention. The analysis of the primary efficacy variable showed a significant treatment difference in favor of Ritalin LA ( $p < 0.0001$ ). A statistically significant treatment effect for 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 12-1.

**Table 12-1 ADHD/DSM-IV Subscales for teachers and parents, change from baseline (ITT population, LOCF analysis)**

	Ritalin LA		Placebo		p-value
	n	Mean change <sup>1</sup> (SD <sup>2</sup> )	n	Mean change <sup>1</sup> (SD <sup>2</sup> )	
<b>CADS-T subscale</b>					
Total	62 <sup>3</sup>	10.7 (15.7)	70 <sup>3</sup>	-2.8 (10.6)	< 0.0001
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
<b>CADS-P subscale</b>					
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

<sup>1</sup>score at end of placebo-washout period minus final score

<sup>2</sup>standard deviation

<sup>3</sup>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.

## 13 Non-clinical safety data

### Pregnancy-embryonal/fetal development

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 maximum recommended human dose (MRHD) of 60 mg. 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 [109]. Exposure (AUC) at 300 mg/kg was 7.5 times the extrapolated exposure at MRHD [147].

Methylphenidate is not teratogenic in rats. Development foetal 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 [92,108,109,147] (see section 9 Pregnancy and breast-feeding).

### Carcinogenesis-mutagenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas (a benign tumour) and, in males only, an increase in hepatoblastomas (a malignant tumour) at daily doses of approximately 60 mg/kg/day (about 35-fold-higher than the MRHD) [109]. There was no overall increase in the number of malignant hepatic tumours [87,88]. The mouse strain used is particularly sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown [89,90].

Similar studies in F344 rats showed no evidence of carcinogenicity [87,88].

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 [91,148] 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 [149], micronuclei in peripheral blood reticulocytes, HPRT mutations and chromosomal aberrations in peripheral blood lymphocytes of rhesus monkeys [150] and pig A locus mutations in adolescent rats [151].

### Juvenile neurobehavioural development

Repeated oral administration of methylphenidate to young rats identified decreased spontaneous locomotor activity at 50 mg/kg/day (29-fold higher than the MRHD), due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females and at the highest dose of

100 mg/kg/day (58-fold higher than the MRHD). The clinical relevance of these findings is unknown [109,110].

Unlike these preclinical findings, long-term administration of methylphenidate in children with ADHD is well tolerated and improves the school performance [111,112]. Thus the clinical experience does not suggest that these learning and behavioural results in rats are clinically relevant.

## **14 Pharmaceutical information**

### **Incompatibilities**

Not applicable.

### **Special Precautions for storage**

#### **Ritalin tablet [10 mg]**

Do not store above 25°C [113,114].

Store in the original package in order to protect from moisture.

Ritalin should be kept out of the reach and sight of children.

#### **Ritalin SR tablet [20 mg]**

Do not store above 30°C [115].

Store in the original package in order to protect from moisture.

Ritalin should be kept out of the reach and sight of children.

#### **Ritalin LA capsules [10mg, 20 mg, 30 mg and 40 mg]**

Do not store above 30°C.

Keep the bottle tightly closed in order to protect from moisture [142,99].

Ritalin should be kept out of the reach and sight of children.

### **Nature and contents of container**

Ritalin tablet [10 mg] and Ritalin SR tablet [20 mg]: blister.

Ritalin LA capsules [10 mg, 20 mg, 30 mg and 40 mg]: HDPE bottles [143,102].

Contents: Country specific.

This is a non-referenced document.