NOVARTIS

RITALIN® 10 Tablets

RITALIN® LA 10/ 20 / 30 /40 Capsules

10 mg methylphenidate hydrochloride per tablet

10 mg, 20 mg, 30 mg and 40 mg methylphenidate hydrochloride per modified-release capsule.

PROFESSIONAL INFORMATION

Document status: Final

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NOVARTIS

PROFESSIONAL INFORMATION

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1. NAME OF THE MEDICINE

RITALIN® 10 Tablets

RITALIN® LA 10 Capsules

RITALIN® LA 20 Capsules

RITALIN® LA 30 Capsules

RITALIN® LA 40 Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is methylphenidate (INN for α-Phenyl-2-piperidineacetic acid methyl ester hydrochloride).

One tablet contains 10 mg methylphenidate hydrochloride.

Each modified-release capsule contains 10 mg, 20 mg, 30 mg and 40 mg methylphenidate hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets and modified-release capsules (Capsules).

RITALIN® 10

White, round, flat, with beveled edges. One side bears the imprint “CG”, the other “A/B” and a score. May contain dark specks. Diameter approximately 7,0 mm; thickness approximately 2,6 mm.

RITALIN® LA 10:

Size # 2, modified-release hard gelatin capsule with a light brown opaque cap and a white opaque body, imprinted with “NVR” in tan ink on the cap and “R10” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

RITALIN® LA 20

Size # 2, modified-release white opaque hard gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R20” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

RITALIN® LA 30

Size # 2, modified-release yellow opaque hard gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R30” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

RITALIN® LA 40

Size # 1, modified-release light brown opaque hard gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R40” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

RITALIN® 10 mg tablets

Attention deficit hyperactivity disorder (ADHD) in children aged 6 years or older.

Narcolepsy in adults.

RITALIN® LA capsules

Attention deficit hyperactivity disorder (ADHD) in children aged 6 years or older, and in adults with ADHD onset in childhood.

The diagnosis should be made according to current DSM criteria or the guidance from International Classification of Diseases (ICD).

4.2. Posology and method of administration

Posology:

The dosage of RITALIN® should be individualised according to the patient's clinical needs and responses.

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 in adults, or for the treatment of ADHD in children. Effective doses in adults may vary and range from 40 to 80 mg per day.

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults (RITALIN® LA only).

If improvement is not observed after appropriate dosage adjustment over a one-month period, RITALIN® should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, RITALIN® should be discontinued.

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 dysrhythmia and psychiatric disorders (see section 4.3 and 4.4).

NARCOLEPSY:

Only the RITALIN® 10 mg formulation is approved in the treatment of narcolepsy in adults.

The average dosage is 20 to 30 mg daily, given in 2 to 3 divided doses. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

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

Periodic assessment of the treatment in ADHD

Medicine treatment should not and need not be indefinite.

RITALIN® should be periodically discontinued to assess the patient's condition. Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

When used in children with ADHD, RITALIN® can usually be discontinued after puberty.

ADHD:

Children and adolescents (6 years and over):

Tablets:

Start with 5 mg once or twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. The total daily dose should be administered in divided doses.

RITALIN® 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. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with RITALIN® LA 10.

Daily dosage above 60 mg is not recommended.

Adults:

Only the RITALIN® LA formulation should be used for the treatment of ADHD in adults.

RITALIN® LA is administered once daily in the morning.

Patients new to methylphenidate: The recommended starting dose of RITALIN® LA 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 conversion to an appropriate recommended dose of RITALIN® LA should be made (see below subsection "*Switching patients to* RITALIN® LA").

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

Switching patients to RITALIN® LA:

The recommended dose of RITALIN® LA should be equal to the total daily dose of the immediate release formulation, not exceeding a total of 60 mg in children and 80 mg in adults. An example in patients being switched from the immediate-released formulation is provided below.

Recommended daily dose when switching patients to RITALIN LA

Previous RITALIN® dose	*Recommended RITALIN® LA dose*
5 mg RITALIN® twice daily	10 mg once daily
10 mg RITALIN® twice daily	20 mg once daily
15 mg RITALIN® twice daily	30 mg once daily
20 mg RITALIN® twice daily	40 mg once daily

For other RITALIN® regimens, clinical judgment should be used when selecting the starting dose. RITALIN® LA dosage may be adjusted at weekly intervals in 10 mg increments for children and in 20 mg increments for adults.

Special populations

Renal impairment

No studies have been performed in renally impaired patients.

Hepatic impairment

No studies have been performed in hepatically impaired patients.

Geriatric patients

No studies have been performed in patients over 60 years of age.

Method of administration:

General recommendations

RITALIN® 10 mg tablets can be taken with or without food.

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). The granules must be swallowed whole and not chewed or crushed.

RITALIN® LA capsules and/or their contents should not be crushed or chewed.

RITALIN® LA administration by sprinkling capsule contents on food:

The capsules may be carefully opened, and the beads sprinkled over soft food.

The food should not be warm because this could affect the modified-release properties of this formulation.

The mixture of medicine and food should be consumed immediately in its entirety. This soft food mixture **should not be chewed** but swallowed only.

The medicine 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.

4.3. Contraindications

Anxiety, tension, agitation, a family history or diagnosis of Tourette's syndrome, hyperthyroidism, glaucoma, phaeochromocytoma.

Pre-existing cardiovascular disorders, including hypertension, angina, arterial occlusive disease; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias, channelopathies (disorders caused by the dysfunction of ion channels) and QT prolongation either congenital, familial or caused by medication (see section 4.4).
During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 2 weeks of discontinuing those medicines, due to risk of hypertensive crisis (see section 4.5).

Known hypersensitivity to methylphenidate or to any of the excipients of RITALIN®.

Pregnancy and Lactation (see section 4.6).

4.4. Special warnings and precautions for use

General:

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

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, in paediatric patients, their appropriateness to the child's age and not simply on the presence of one or more abnormal behavioural characteristics.

RITALIN® should not be used for the treatment of attention-deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

Chronic abuse of RITALIN® can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur. Abuse of RITALIN® may prove a problem in predisposed patients e.g. in emotionally unstable individuals or those with a history of drug dependence or alcoholism.

RITALIN® should therefore be used only under medical supervision. Clinical data indicate that children given RITALIN® are not more likely to abuse drugs than adolescents or adults.

Cardiovascular:

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems:

Sudden death has been reported in association with the use of RITALIN® at usual doses in patients with pre-existing structural cardiac abnormalities or other serious heart problems. A causal relationship with RITALIN® has not been established since some of these conditions alone may carry an increased risk of sudden death. RITALIN® 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 its sympathomimetic effects. Before initiating RITALIN® treatment, patients should be assessed for pre-existing cardiovascular disorders such as a congenital long QT syndrome, or a family history of sudden death and ventricular dysrhythmia (see section 4.2).

Misuse and Cardiovascular Events:

Misuse of RITALIN®, may be associated with sudden death and other serious cardiovascular adverse events.

Cardiovascular conditions:

RITALIN is contraindicated in patients with hypertension. 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 and severe cardiovascular disorders (see section 4.3).

Blood pressure should be monitored at appropriate intervals in all patients taking RITALIN®. Patients who develop symptoms suggestive of cardiac disease during RITALIN® treatment should undergo a prompt cardiac evaluation.

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 4.5).

Psychiatric:

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing RITALIN®. Prior to initiating treatment with RITALIN®, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section 4.2). Treatment of ADHD with 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 recommended therapeutic doses of RITALIN (see section 4.8). Medical practitioners should consider treatment discontinuation.

Aggressive behaviour: Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during RITALIN® therapy. Medical practitioners 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 and caregivers of patients should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms appear.
The medical practitioner should initiate appropriate treatment of any underlying psychiatric condition and consider a possible discontinuation or 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 4.8). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of RITALIN® for ADHD treatment. RITALIN® is contraindicated in case of diagnosis or family history of Tourette's syndrome (see section 4.3). Patients should be regularly monitored for the emergence or worsening of tics during treatment with RITALIN®.

Serotonin syndrome**:** Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of RITALIN® and serotonergic medicines 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, diarrhoea).

Prompt recognition of these symptoms is important so that treatment with RITALIN® and serotonergic medicines can be immediately discontinued and appropriate treatment instituted (see section 4.5).

Acute Angle Closure Glaucoma: There have been reports of acute angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, Ritalin-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

Increased Intraocular Pressure and Glaucoma: There have been reports of an elevation of intraocular pressure (IOP) and glaucoma (including open angle glaucoma and angle closure glaucoma) associated with methylphenidate treatment (see section 4.8). Close monitoring of Ritalin-treated patients with a history of abnormally increased IOP or glaucoma is recommended.

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

Growth retardation:

Reduced weight gain and slight growth retardation have been reported with the long-term use of RITALIN® (see section 4.8). Growth and weight should be monitored during treatment with

RITALIN, and patients who are not growing or gaining height or weight as expected or are losing weight may need to have their treatment interrupted and adjusted.

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 4.8).

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. If seizure frequency increases, RITALIN® should be discontinued.

Drug abuse and dependence:

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.

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 RITALIN® withdrawal, since this may unmask depression as well as the effects of chronic overactivity. Some patients may require long-term follow-up.

Paediatric patients under 6 years of age:

RITALIN® is not indicated in children less than six years of age.

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 the medical practitioner assessment of the chronicity and severity of the child's symptoms and, their appropriateness to the child's age. Prescription should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with RITALIN® is not indicated.

Lactose intolerance:

RITALIN® 10 tablets contain lactose. Patients with rare hereditary problems of lactose intolerance e.g. galactosaemia or severe lactase deficiency should not use RITALIN® 10 tablets.

RITALIN® LA capsules contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take RITALIN® LA capsules.

RITALIN® 10 (containing lactose) and RITALIN® LA (containing sucrose) may have an effect on the glycaemic control of patients with diabetes mellitus.

Medicine/Laboratory test:

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

4.5. Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

RITALIN® is not metabolised 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® co-administration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

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

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

Pharmacodynamic interactions

Anti-hypertensive medicines

RITALIN® may decrease the effectiveness of medicines used to treat hypertension.

Use with medicines that elevate blood pressure

RITALIN® should be used with caution in patients being treated with medicines that elevate blood pressure (see paragraph on *Cerebrovascular Conditions* under section 4.4). Because of possible hypertensive crisis, RITALIN® is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the central nervous system adverse reactions of RITALIN®. It is advisable for patients to abstain from alcohol during treatment.

Use with dopaminergic medicines

As an inhibitor of dopamine reuptake, RITALIN® 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). Concomitant use of RITALIN® with antipsychotics is not recommended due to its counteracting mechanism of action. If upon medical assessment the combination is deemed necessary, monitoring for extrapyramidal symptoms (EPS) is recommended, as the concomitant use of methylphenidate with antipsychotics may increase the risk of EPS when there is a change (increase or decrease) in dosage of either or both medications.

Use with anaesthetics

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

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

Serious adverse events including sudden death may occur in concomitant use with clonidine or dexmedetomidine, although no causality for the combination has been established.

Use with serotonergic medicines

The concomitant use of RITALIN® and serotonergic medicines is not recommended as this may lead to the development of serotonin syndrome (see section 4.4). Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

4.6. Fertility, pregnancy and lactation

Pregnancy

RITALIN® is contraindicated in pregnancy and lactation as safety has not been demonstrated (see section 4.3).

Lactation

Mothers on RITALIN® should not breastfeed their infants.

4.7. Effects on ability to drive and use machines

RITALIN® may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side-effects (see section 4.8). Patients experiencing such side-effects should refrain from driving, operating machines or engaging in other potentially hazardous activities.

4.8. Undesirable effects

Nervousness and insomnia are very common adverse reactions. These usually occur at the beginning of RITALIN® treatment and may be reduced by decreasing the dose and omitting the medicine in the afternoon or evening.

Decreased appetite is very common.

Abdominal pain, nausea and vomiting are common to very common.

Reports of 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.

Tabulated summary of adverse reactions

Adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

In addition, the corresponding frequency category for each adverse 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: Adverse reactions reported with RITALIN® use

Infections and infestations:

Very common: Nasopharyngitis*

Blood and the lymphatic system disorders:

Very rare: Leucopenia, thrombocytopenia, anaemia

Immune system disorders:

Very rare: Hypersensitivity reactions

Metabolism and nutrition disorders:

Very Common: Decreased appetite**

Rare: 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, choreo-athetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents

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: Growth retardation during prolonged use in children

Investigations:

Common: Weight decreased*

Vascular disorders:

Common: Raynaud's phenomenon**, peripheral coldness**

* ADRs reported from 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.

The list below shows reported post-marketing adverse reactions

Blood and lymphatic disorders:

Pancytopenia

Immune system disorders:

Hypersensitivity reactions, including angioedema and anaphylaxis

Psychiatric disorders:

Irritability, affect lability, abnormal behaviour or thinking abnormal, anger, mood altered, mood swings, hypervigilance, mania, disorientation, libido disorder[1], apathy, stereotypy[2], change in sustained attention[3], confusional state, drug abuse[4] and drug dependence[4].

Nervous system disorders:

Reversible ischaemic neurological deficit, migraine

Eye disorders:

Diplopia, mydriasis, visual impairment[5]

Ear and labyrinth disorders

Auricular swelling[6]

Cardiac disorders:

Cardiac arrest, myocardial infarction

Respiratory, thoracic and mediastinal disorders:

Laryngeal pain[7], dyspnoea, epistaxis

Gastrointestinal disorders:

Diarrhoea, constipation

Skin and subcutaneous tissue disorders:

Angioedema, erythema, fixed eruption[8]

Musculoskeletal, connective tissue and bone disorders:

Myalgia, muscle twitching

Renal and urinary disorders:

Haematuria

Reproductive system and breast disorders:

Gynaecomastia, erectile dysfunction

General disorders and administration site conditions:

Chest pain, fatigue, sudden cardiac death

Investigations:

Cardiac murmur, increased intraocular pressure

[1] Includes libido decreased

[2] Includes repetitive behaviours

[3] Includes overfocusing and hyperfocusing

[4] Cases of abuse and dependence have been described, more often with immediate-release formulations

[5] Includes visual disturbance

[6] Related to hypersensitivity reactions

[7] Includes pharyngolaryngeal pain

[8] Includes fixed drug eruption

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

The following adverse reactions have been derived from post-marketing experience with RITALIN® 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 reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Reproductive system and breast disorders

Priapism

Psychiatric disorders

Dysphemia, suicidal ideation or attempt (including completed suicide)

Renal and urinary disorders

Enuresis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose

Signs and symptoms:

Vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac dysrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment:

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.

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events e.g. hypertensive crisis, cardiac dysrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the practitioner should consult a certified Poison Control Centre or current toxicological publication.

Supportive measures include protection of the patient against self-injury and against external stimuli that would exacerbate the overstimulation already present. If the overdose is oral and the patient is conscious, administration of activated charcoal is recommended.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required to reduce hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdosage of RITALIN® has not been established.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological Classification : A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: psychostimulants - ATC code: NO6B AO4.

5.1. Pharmacodynamic properties

Methylphenidate is a racemate, consisting of a 1:1 mixture of d-methylphenidate and l-methylphenidate.

Methylphenidate is a central nervous system stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood, 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.

The effect of treatment with 40 mg dexmethylphenidate hydrochloride, the pharmacologically active d-enantiomer of methylphenidate, on QT/QTc interval was evaluated in a study in 75 healthy adult volunteers. The maximum mean prolongation of QTcF intervals was < 5 millisecond (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.

5.2. Pharmacokinetic properties

***Absorption*:**

Methylphenidate 10:

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 absorption (food increases the peak plasma concentration (C_{max}) by 23% and the area under the concentration-time curve (AUC) by 15%). Peak plasma concentrations of approximately 40 nmol/litre (11 ng/mL) are attained, on average 1 to 2 hours after administration. The peak plasma concentrations, however, vary markedly from one person to another. The area under the plasma concentration curve (AUC),

as well as the peak plasma concentration (C_{max}), is proportional to the size of the dose administered.

Methylphenidate LA 10, methylphenidate LA 20, methylphenidate LA 30, and methylphenidate LA 40:

Following oral administration of methylphenidate hydrochloride (modified-release capsules) to children diagnosed with ADHD and adults, methylphenidate plasma concentration-time profiles show a bi-modal profile (i.e. two distinct peaks approximately four hours apart). The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for methylphenidate LA given once a day compared to methylphenidate tablets given twice a day. Methylphenidate hydrochloride may be administered with or without food. There were no differences in the bioavailability of methylphenidate 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.

For patients unable to swallow the capsule, the contents may be sprinkled on soft food and administered (see section 4.2).

Distribution:

In the blood, methylphenidate and its metabolites are distributed in the plasma (57 %) and in the erythrocytes (43 %). Methylphenidate and its metabolites have a low plasma protein-binding (10 to 33 %).

The apparent distribution volume has been calculated as 13,1 L/kg after an oral dose; the volume of distribution after intravenous dose (Vss) is 2,23 L/kg for the racemate in healthy adult volunteers. The volume of distribution was 2,65 ± 1,11 L/kg for dextromethylphenidate (D-MPH) and 1,80 ± 0,91 L/kg for levomethylphenidate (L-MPH).

Methylphenidate is excreted in breast milk.

***Elimination*:**

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours, and 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 the urine and 1 to 3 % in the faeces in the form of metabolites within 48 to 96 hours. Unchanged methylphenidate appears in the urine only in small quantities (< 1 %). The bulk of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (PPAA, 60 to 86 %).

***Biotransformation*:**

Peak plasma concentrations of PPAA (ritalinic acid) are attained approximately 2 hours after administration of methylphenidate and are 30 to 50 times higher than those of the unchanged substance. The half-life of PPAA is roughly twice as long as that of methylphenidate, and the mean systemic clearance is 0,17 L/h/kg.

Characteristics in patients:

There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and healthy adult volunteers.

Renal excretion of the unchanged methylphenidate is hardly diminished at all in the presence of impaired renal function; however, renal excretion of PPAA is reduced.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

RITALIN® tablet (10 mg): calcium phosphate tribasic, lactose monohydrate, wheat starch, gelatine, magnesium stearate and talc.

Contains sugar: Lactose.

RITALIN® LA capsules (10 mg, 20 mg, 30 mg and 40 mg): ammonio methacrylate copolymer type B, black iron oxide (E 172) (10 mg, and 40 mg capsules only), gelatine, methacrylic acid copolymer type A, macrogol 6000, red iron oxide (E 172) (10 mg, and 40 mg capsules only), sugar spheres, talc, titanium dioxide (E 171), triethyl citrate and yellow iron oxide (E 172) (10 mg, 30 mg and 40 mg capsules only).

Contains sugar: Sucrose.

6.2. Incompatibilities

None known.

6.3. Shelf life

RITALIN® 10; RITALIN® LA 10: 24 months

RITALIN® LA 20; RITALIN® LA 30; RITALIN® LA 40: 36 months

6.4. Special precautions for storage

RITALIN® 10:

Store at or below 25 °C and protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

RITALIN® LA capsules:

Store at or below 25° C. Keep the container tightly closed. Protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5. Nature and contents of container

RITALIN® 10 is supplied as tablets of 10 mg in blister packs of 30.

RITALIN® LA is available in white HDPE bottles containing 30 and 100 modified-release capsules.

6.6. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LIMITED

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

+27113476600

8. REGISTRATION NUMBERS

RITALIN® 10	B/1.2/1610
RITALIN® LA 10	44/1.2/0594
RITALIN® LA 20	36/1.2/0186
RITALIN® LA 30	36/1.2/0187
RITALIN® LA 40	36/1.2/0188

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

RITALIN® 10:	14 October 1997
RITALIN® LA 10:	30 September 2011
RITALIN® LA 20, 30, 40:	06 August 2002

10. DATE OF REVISION OF THE TEXT

12 August 2025

RITALIN® 10

Namibia	04/1.2/0552	NS4	**Manufacturer:** Siegfried Barbera, S.L., Ronda de Santa Maria, 158, 08210 Barberà del Vallès, (Barcelona), Spain
Botswana	B9302455	S1B	