AUSTRALIAN PRODUCT INFORMATION RITALIN® 10/RITALIN® LA (methylphenidate)

DRUG DEPENDENCE: Ritalin should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow up.

1. NAME OF THE MEDICINE

Methylphenidate hydrochloride.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ritalin 10 contain methylphenidate hydrochloride 10 mg.

Ritalin LA modified release capsules contain 10 mg, 20 mg, 30 mg, 40 mg or 60 mg of methylphenidate hydrochloride.

Ritalin 10 contains lactose, sugars, milk products, lactitol, gluten and sulfur dioxide. Ritalin LA contains sucrose.

For the full list of the excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Ritalin 10 tablets are immediate release white tablets that are scored and marked AB and CG on the reverse.

Ritalin LA are modified release capsules that presented as follows:

10 mg cotaining white to off-white beads in a light brown opaque hard gelatin capsule with the imprint of NVR on the cap and R10 on a white opaque body in tan-coloured ink.

20 mg containing white to off-white beads in a white opaque hard gelatin capsule with imprint NVR on the cap and R20 on body in tan-coloured ink.

30 mg containing white to off-white beads in a yellow opaque hard gelatin capsule with the imprint NVR on cap and R30 on body in tan-coloured ink.

40 mg containing white to off-white beads in a light brown opaque hard gelatin capsule with the imprint NVR on cap and R40 on body in tan-coloured ink.

60 mg containing white to off-white beads in a light brown opaque cap and a yellow opaque body hard gelatin capsule with imprint NVR on cap and R60 on body in tan-coloured ink. Not all presentations are available.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ritalin 10 tablets and Ritalin LA capsules are indicated for the treatment of ADHD. Ritalin 10 tablets are also indicated for the treatment of narcolepsy.

Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD was previously known as attention-deficit disorder. Other terms used to describe this behavioural syndrome include: minimal brain dysfunction in children, hyperkinetic child syndrome, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children.

Ritalin 10 / Ritalin LA are indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational and social) for patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis.

Special diagnostic considerations for ADHD in children

The aetiology of this syndrome is unknown and there is no single diagnostic test. Adequate diagnosis requires the use, not only of medical, but also of psychological, educational and social resources. Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and an abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in children who exhibit symptoms secondary to environmental factors (e.g. child abuse in particular) or primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medicine will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Continuation of treatment in adolescent and special diagnostic considerations for ADHD in adults

There is limited information to guide clinicians about how long older adolescents should continue to receive treatment with drugs for attention deficit hyperactivity disorder (ADHD). The decision should be based on the extent to which symptoms of ADHD and social functioning have improved to a point that medication is no longer needed. If older adolescents have been largely symptom-free for a year and are functioning well, a trial without medication is warranted. This should be undertaken at times of low stress such as during holidays or in a period when a school routine is well established.

ADHD needs to be considered in adults who present with longstanding symptoms suggestive of ADHD (inattention, impulsivity, disorganisation) that appear to have started in childhood and are persisting into adult life. Further, people with personality disorder and/or problems with drug use accompanied by a significant level of impulsivity and inattention should be referred for evaluation by a psychiatrist with the training and skills required to assess and treat ADHD. This expertise is necessary due to the overlap of ADHD symptoms with anxiety, mood and personality disorders.

Narcolepsy

The symptoms include daytime sleepiness, inappropriate sleep episodes and rapidly occurring loss of voluntary muscle tone. Ritalin 10 is effective for symptoms of sleepiness but not for loss of voluntary muscle tone.

4.2. DOSE AND METHOD OF ADMINISTRATION

Pre-treatment Screening

Treatment should only be initiated by specialist physicians with experience in the use of the drug. Before initiating Ritalin 10/ Ritalin LA treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular arrhythmia and psychiatric disorders. Weight and height should also be measured before treatment and documented on a growth chart (4.3 CONTRAINDICATIONS and4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Dosage

The dosage of Ritalin 10/ Ritalin LA should be individualised according to the patient's clinical needs and responses.

Treatment with Ritalin 10/Ritalin LA should be initiated at a low dose, with increments at weekly intervals.

ADHD

In the treatment of ADHD, an attempt should be made to time administration of the drug to coincide with periods of greatest academic, behavioural or social difficulties for the patient.

If symptoms do not improve after dose titration over an one-month period, 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. A small evening dose of Ritalin 10 mg tablet may help solve this problem.

Periodic assessment of the treatment in ADHD

Drug treatment does not need to be indefinite. Physicians should periodically re-evaluate the treatment with trial periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued. When used in children with ADHD, treatment can usually be discontinued during or after puberty.

If therapy is interrupted for reasons other than those stated above, it should not be restarted at the dose that had been reached prior to treatment interruption, but should be re-titrated.

Children and adolescents (6 years and over)

Ritalin 10 tablets

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

In some children with ADHD, sleeplessness may occur as the effect of the drug wears off. On rare occasions, an additional dose at about 8.00 p.m. may help; a trial dose may help to clarify the issue in an individual case, if the symptom warrants treatment.

Ritalin LA capsules

Maximum daily doses

Daily doses above 60 mg are not recommended for the treatment of ADHD in children and adolescents.

Patients new to methylphenidate

The recommended starting dose of Ritalin LA who are currently **not** taking methylphenidate is 20 mg once daily.

When in the judgement of the clinician a lower initial dose is appropriate treatment may begin with Ritalin LA 10 mg.

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 switch to an appropriate recommended dose of Ritalin LA should be made (see Switching patient's treatment from Ritalin 10 to Ritalin LA capsules).

Adults

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

Ritalin LA capsules

Maximum daily doses

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults.

Patients new to methylphenidate

The recommended starting dose of Ritalin LA who are currently **not** 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 Switching patient's treatment from Ritalin 10 to Ritalin LA capsules).

There are no differences recommended in dosing between male and female adult patients.

Use in Elderly

Use of Ritalin LA in patients over 60 years of age has not been studies in controlled trials.

Switching patient's treatment from Ritalin 10 to Ritalin LA capsules

The recommended dose of Ritalin LA should be equal to the total daily dose of the immediate-release formulation not exceeding a total dose of 60 mg in children and 80 mg in adults. Examples involving switch from Ritalin 10 immediate-release tablets are provided in Table 1.

Table 1: Recommended daily dose when switching treatment to Ritalin LA

Previous dose of Ritalin 10 tablets	Recommended dose of Ritalin LA capsules
5 mg twice daily	10 mg daily
10 mg twice daily	20 mg daily
15 mg twice daily	30 mg daily
20 mg twice daily	40 mg 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 for children and in 20 mg increments for adults.

Narcolepsy

Ritalin 10

Adults

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

Dosing for each patient requires titration to control symptoms. Single doses greater than 20 mg are associated with sympathomimetic side effects. Therefore, the average single dose should be less than 20 mg. A maximum total dose of 60 mg/day may be required.

Maximum daily doses

A maximum daily dose of 60 mg should not be exceeded for the treatment of narcolepsy.

Administration

Ritalin 10 tablets

The rate of absorption and, therefore, onset of action is faster when Ritalin 10 tablets are taken with food. Dosage should, therefore, be standardised in relation to food to ensure consistency of effect.

Doses should be administered 1 to 2 hours before the maximum effect is required.

Ritalin LA

Ritalin LA capsules should be administered orally once daily in the morning.

Ritalin LA may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of soft food (see specific instructions below). Ritalin LA capsules and/or their contents should not be crushed, chewed or divided.

The capsules may be administered with or without food. A high fat breakfast may slow the rate of absorption and therefore onset of action. Dosage should, therefore, be standardised in relation to food to ensure consistency of effect.

Ritalin LA administered as a single daily dose provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of immediate release tablets administered twice daily.

Sprinkling Ritalin LA capsule contents on food

Carefully open the Ritalin LA capsule(s) and sprinkle the beads over applesauce. The food should not be warm because it could affect the modified-release properties of the formulation. All of the mixture of drug and food should be immediately swallowed, unchewed. The drug and food mixture should **not** be stored for future use.

4.3 CONTRAINDICATIONS

Ritalin is contraindicated in patients with the following:

- anxiety and tension states
- agitation
- a family history or diagnosis of Tourette's syndrome
- glaucoma
- hyperthyroidism
- pre-existing cardiovascular disorders including uncontrolled hypertension, angina pectoris, arterial occlusive disease especially coronary arteries; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, cardiac arrhythmia and channelopathies (disorders caused by the dysfunction of ion channels)
- treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase (MAO) inhibitor (hypertensive crises may result)
- phaeochromocytoma
- known drug dependence or alcohol abuse
- severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency, since Ritalin might worsen these conditions
- known hypersensitivity to methylphenidate or to any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only after detailed history taking and evaluation of the patient. The decision to prescribe methylphenidate should depend on the physician's assessment of the chronicity and severity of the symptoms and in paediatric patients, the appropriateness to the child's age. Prescription should not depend solely on the presence of isolated behavioural characteristics. When the symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Stimulants, including non-pharmacotherapeutics (e.g., energy drinks, caffeine) should be used with caution in patients during treatment with Ritalin.

Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems

It is essential that patients with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a cardiologist before initiating treatment. On-going cardiological supervision should be maintained throughout treatment in these patients.

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems.

Stimulant products, including methylphenidate, generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may increase the risk of sudden death due to the sympathomimetic effects of a stimulant drug. Before initiating methylphenidate treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Cardiovascular Conditions

Ritalin is contraindicated in patients with severe 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. Severe cardiovascular disorders are contraindicated (see 4.3 CONTRAINDICATIONS).

Methylphenidate should be used cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking methylphenidate, especially in those with hypertension. Patients who develop symptoms

suggestive of cardiac disease during methylphenidate treatment should undergo a prompt cardiac evaluation.

Children, adolescents, or adults who are being considered for treatment with stimulant medicine should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Misuse and Cardiovascular Events

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

Cerebrovascular

Cerebrovascular conditions

Patients with pre-existing central nervous system (CNS) abnormalities, e.g., cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with Ritalin. Patients with additional risk factors (history of cardiovascular disease, concomitant medicine that elevates blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with Ritalin (see 4.4 PRECAUTIONS – Cardiovascular Conditions and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Psychiatric Conditions

Ritalin should not be used to treat severe depression or for the prevention or treatment of normal fatigue states. In psychotic patients administration of methylphenidate may exacerbate symptoms of behaviour disturbance and thought disorder.

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with methylphenidate, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see 4.2 DOSE AND METHOD OF 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. Methylphenidate should not be used as treatment for severe depression of either exogenous or endogenous origin.

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 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Physicians should consider treatment discontinuation if psychotic symptoms occur.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

Aggressive behaviour

Ritalin has been causally associated with aggression. Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Ritalin. 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 and caregivers of patients should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in bahaviour and to seek medical advice immediately if these symptoms appear. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible discontinuation or change in the ADHD treatment.

Motor and verbal tics

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Therefore, clinical evaluation for tics in patients should precede use of stimulant medicine. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of methylphenidate for ADHD treatment. Ritalin is contraindicated in case of diagnosis or family history of Tourette's syndrome (see 4.3 CONTRAINDICATIONS). Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.

Serotonin syndrome

Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome. The symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Prompt recognition of these symptoms is important so that treatment with methylphenidate and serotonergic drugs can be immediately discontinued and appropriate treatment instituted (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Paediatric use

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

Growth retardation

Moderately reduced weight gain and slight growth retardation have been reported with the long term use of stimulants, including methylphenidate, in children (see 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Growth should be monitored as clinically necessary during treatment with methylphenidate, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Careful follow up of weight and height in children aged 7 to 10 years who were randomised to either methylphenidate or non-medicine treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medicine treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

The retardation of growth referred to under "4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS" is usually followed by catch-up growth when the medicine is discontinued. In order to minimise such complications, drug-free periods over weekends, school holidays and long vacations are advocated by some specialists.

Fatigue

Methylphenidate should not be employed for the prevention or treatment of normal fatigue states.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsion threshold in patients with a history of seizures, with prior EEG abnormalities in the absence of seizures and, rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, the drug should be discontinued.

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. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including Ritalin and Ritalin LA, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, have been observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g. rheumatology referral) may be appropriate for certain patients.

Drug abuse and dependence

Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because they may increase the dosage on their own initiative. Chronic abuse can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially in response to parenteral abuse.

Clinical data indicate that children given Ritalin are not more likely to abuse drugs as adolescents or adults. Methylphenidate abuse or dependence does not appear to be a problem in adolescents or adults who were treated with methylphenidate for ADHD as children.

Use with alcohol

Alcohol may exacerbate the CNS adverse reactions of psychoactive drugs, including methylphenidate. Therefore, it is advisable for patients to abstain from alcohol during treatment.

Withdrawal

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

Haematological effects

Data on safety and efficacy of long-term use of methylphenidate are not complete. Patients requiring long-term therapy should be carefully monitored and periodic complete blood counts, differential and platelet counts are advisable during prolonged therapy. In the event of haematological disorders appropriate medical intervention should be considered (see 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anti-hypertensive drugs

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

Use with drugs that elevate blood pressure

Methylphenidate should be used with caution in patients being treated with drugs that elevate blood pressure due to the risk of severe hypertension (see 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Cerebrovascular Conditions).

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 4.3 CONTRAINDICATIONS).

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)

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

Use with 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).

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 serotonergic drugs

The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome (see 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Methylphenidate has been shown to increase extracellular serotonin and noradrenaline and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic interactions

Ritalin is not metabolized by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on Ritalin pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate did not relevantly inhibit in vitro cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A.

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

Case reports have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbitone, primidone, phenytoin), phenylbutazone and tricyclic antidepressants (imipramine, desipramine), but pharmacokinetic interactions were not confirmed when explored at higher sample sizes. Reduction in the dosage of these drugs may be required when they are given concomitantly with methylphenidate.

Serious adverse events 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of methylphenidate on fertility are available.

Women of child-bearing potential

Methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks (see Use in Pregnancy).

Use in pregnancy

Category D

The safety of methylphenidate for use during human pregnancy has not been established. Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations in women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.Methylphenidate should not be prescribed for pregnant women unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

As a general rule no drugs should be taken during the first 3 months of pregnancy, and the benefits and risks of taking drugs should be carefully considered throughout the whole of the pregnancy.

Use in Lactation

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5. For safety reasons, mothers taking

methylphenidate should refrain from breast-feeding their infants. A decision should be made by the prescriber whether the mother must abstain from breast-feeding or abstain from methylphenidate therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ritalin may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects reported during clinical trials

Children

A randomised, double-blind, placebo-controlled parallel group clinical study (Protocol 07) was conducted to evaluate the efficacy and safety of Ritalin LA in children aged 6 - 12 years with ADHD. In the double-blind treatment phase of this study, Ritalin LA was administered once daily for up to two weeks at individually titrated doses in the 10 – 40 mg range. The incidence of treatment-emergent adverse events reported during the double-blind treatment phase is summarised in Table 2. Adverse events reported with an incidence ≥ 2% in all treated subjects in Protocol 07 (including adverse events during the titration period and placebo-washout period) are included in Table 3.

Table 2: Treatment-emergent adverse events[1] with an incidence of ≥ 2% in the two-week double-blind treatment phase of a placebo controlled clinical study of Ritalin LA in children (Protocol 07)

Adverse event	Ritalin LA N = 65 (%)	Placebo N = 71 (%)	Adverse event	Ritalin LA N = 65 (%)	Placebo N = 71 (%)
Total	16 (24.6)	17 (23.9)	Headache	1 (1.5)	2 (2.8)
Anorexia	2 (3.1)	0 (0.0)	Sore throat	0 (0.0)	3 (4.2)
Insomnia	2 (3.1)	0 (0.0)	Vomiting	0 (0.0)	2 (2.8)

[1] Adverse events, regardless of study drug relationship, reported in 2% or more subjects in either group.

A subject with multiple occurrences of an AE under one treatment group is counted only once in the AE category for that treatment.

Table 3: Adverse events[1] with an incidence ≥ 2% in all treated patients (including adverse events during the titration period and placebo-washout period) in a placebo controlled clinical study of Ritalin LA in children (Protocol 07)

Adverse event	Ritalin LA N = 161 (%)	Adverse event	Ritalin LA N = 161 (%)
Total	103 (64.0)	URTI	7 (4.3)
Headache	26 (16.1)	Vomiting	6 (3.7)

Adverse event	Ritalin LA N = 161 (%)	Adverse event	Ritalin LA N = 161 (%)
Insomnia	17 (10.6)	Cough	5 (3.1)
Upper abdominal pain	12 (7.5)	Dermatitis	5 (3.1)
Anorexia	11 (6.8)	Ear infection	5 (3.1)
Appetite, decreased	11 (6.8)	Nausea	5 (3.1)
Nasopharyngitis	11 (6.8)	Joint sprain	4 (2.5)
Irritability	8 (5.0)	Pyrexia	4 (2.5)
Lethargy	8 (5.0)		

[1] Adverse events, regardless of study drug relationship, reported in 2% or more subjects.

A subject with multiple occurrences of an AE under one treatment group is counted only once in the AE category for that treatment.

Adults

Ritalin LA was evaluated in a randomized, double-blind, placebo-controlled, multicentre core study (D2302) in the treatment of 725 adult patients (395 male and 330 female) diagnosed with ADHD. Maintenance of effect of Ritalin LA was evaluated in a 6-month maintenance study (D2302E1) in 298 patients. The incidence of adverse events reported during the core study and extension studies are summarised in Table 4 and Table 5 respectively.

Table 4: Number (%) of patients with most frequent AEs during Period 1 by preferred term and treatment (≥5% for any group) (Safety Analysis Set for Period 1)

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n (%)	
Total no. of patients with AEs	131	(72.8)	13	(74.0)	136	(75.1)	401	(74.0)	108	(60.0)
Decreased appetite	39	(21.7)	49	(27.1)	48	(26.5)	136	(25.1)	8	(4.4)
Headache	39	(21.7)	42	(23.2)	30	(16.6)	111	(20.5)	30	(16.7)
Dry mouth	34	(18.9)	39	(21.5)	37	(20.4)	110	(20.3)	4	(2.2)

Nausea	15	(8.3)	20	(11.0)	23	(12.7)	58	(10.7)	9	(5.0)
Nasopharyngitis	22	(12.2)	15	(8.3)	17	(9.4)	54	(10.0)	17	(9.4)
Insomnia	13	(7.2)	18	(9.9)	13	(7.2)	44	(8.1)	7	(3.9)
Hyperhidrosis	12	(6.7)	14	(7.7)	17	(9.4)	43	(7.9)	5	(2.8)
Palpitations	8	(4.4)	15	(8.3)	16	(8.8)	39	(7.2)	1	(0.6)
Fatigue	11	(6.1)	16	(8.8)	11	(6.1)	38	(7.0)	11	(6.1)
Dizziness	12	(6.7)	9	(5.0)	11	(6.1)	32	(5.9)	5	(2.8)
Irritability	11	(6.1)	12	(6.6)	9	(5.0)	32	(5.9)	8	(4.4)
Anxiety	8	(4.4)	11	(6.1)	10	(5.5)	29	(5.4)	1	(0.6)
Initial insomnia	9	(5.0)	4	(2.2)	15	(8.3)	28	(5.2)	2	(1.1)
Restlessness	9	(5.0)	10	(5.5)	7	(3.9)	26	(4.8)	5	(2.8)
Tachycardia	6	(3.3)	10	(5.5)	10	(5.5)	26	(4.8)	0	(0.0)
Abdominal pain upper	6	(3.3)	3	(1.7)	13	(7.2)	22	(4.1)	7	(3.9)
Diarrhoea	4	(2.2)	4	(2.2)	9	(5.0)	17	(3.1)	12	(6.7)

Table 5: Adverse events with an incidence ≥ 2 % in all D2302E1 patients (regardless of study drug relationship) by primary system organ class and mean daily dose

Primary System Organ Class	**Ritalin LA mean daily dose**			
	≤ 40 mg N=85 (%)	**> 40-60 mg N=104 (%)**	**> 60 mg N=109**	**All extension patients N=298 (%)**
Any primary system organ class	59 (69.4)	78 (75.0)	71 (65.1)	208 (69.8)
Cardiac Disorders	4 (4.7)	7 (6.7)	4 (3.7)	15 (5.0)
Ear and Labyrinth Disorders	1 (1.2)	3 (2.9)	2 (1.8)	6 (2.0)
Eye Disorders	1 (1.2)	3 (2.9)	3 (2.8)	7 (2.3)
Gastrointestinal Disorders	20 (23.5)	21 (20.2)	16 (14.7)	57 (19.1)

Primary System Organ Class	Ritalin LA mean daily dose			
	≤ 40 mg N=85 (%)	> 40-60 mg N=104 (%)	> 60 mg N=109	All extension patients N=298 (%)
General Disorders and Administration Site Condition	11 (12.9)	8 (7.7)	4 (3.7)	23 (7.7)
Immune System Disorders	3 (3.5)	1 (1.0)	2 (1.8)	6 (2.0)
Infections and Infestations	29 (34.1)	47 (45.2)	38 (34.9)	114 (38.3)
Injury, Poisoning and Procedural Complications	2 (2.4)	3 (2.9)	5 (4.6)	10 (3.4)
Investigations	0 (0.0)	6 (5.8)	6 (5.5)	12 (4.0)
Metabolism and Nutrition Disorders	4 (4.7)	12 (11.5)	8 (7.3)	24 (8.1)
Musculoskeletal and Connective Tissue Disorders	5 (5.9)	15 (14.4)	7 (6.4)	27 (9.1)
Nervous System Disorders	20 (23.5)	23 (22.1)	21 (19.3)	64 (21.5)
Psychiatric Disorders	19 (22.4)	29 (27.9)	14 (12.8)	62 (20.8)
Reproductive System and Breast Disorders	3 (3.5)	3 (2.9)	3 (2.8)	9 (3.0)
Respiratory, Thoracic and Mediastinal Disorders	6 (7.1)	11 (10.6)	6 (5.5)	23 (7.7)
Skin and Subcutaneous Tissue Disorders	5 (5.9)	5 (4.8)	5 (4.6)	15 (5.0)
Vascular Disorders	4 (4.7)	3 (2.9)	5 (4.6)	12 (4.0)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in total row.

The AE profile seen in the maintenance period was similar to that observed in the core study. No unexpected SAEs or AEs were observed in this extension study and the commonly observed AEs were expected and driven by the pharmacologic activity.

The most frequently affected primary SOCs (≥ 10 % in all extension patients) starting in the extension study were infections and infestations, nervous system disorders, psychiatric disorders, and gastrointestinal disorders. There was no evidence of toxicity to any organ system. The most commonly reported individual AEs (≥ 5.0 % in any dose group) during the extension study were nasopharyngitis (19.1 %), headache (14.1 %), decreased appetite (7.7 %), dry mouth (6.7 %) and nausea (5.0 %).

Post-marketing Experience

Nervousness and insomnia are very common adverse reactions which occur at the beginning of Ritalin/Ritalin LA treatment and are usually controlled by reducing the dosage and omitting the drug in the afternoon or evening.

Loss of appetite is very common but usually transient. Abdominal pain, insomnia and tachycardia are common, usually at the beginning of treatment and may be alleviated by concomitant food intake.

Tabulated summary of adverse drug reactions

Adverse drug reactions listed in Table 6 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ≥10%; common ≥1% to <10%; uncommon ≥0.1% to <1%; rare ≥0.01% to <0.1%; very rare <0.01%.

Table 6: Adverse reactions reported with Ritalin/Ritalin LA use

Infections and Infestations	
Very common	Nasopharyngitis
Blood and the lymphatic system disorders	
Very rare	Leucopenia, thrombocytopenia, anaemia
Immune system disorders	
Very rare	Hypersensitivity reaction, including angioedema[1] and anaphylaxis
Metabolism and nutrition disorders	
Very common	Decreased appetite
Rare	Moderately reduced weight gain during prolonged use in children
Psychiatric disorders	
Very common	Nervousness, insomnia, irritability
Common	Anxiety, restlessness, sleep disorder, agitation, depression, aggression, bruxism
Very rare	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood
Nervous system disorders	
Common	Dyskinesia, tremor, headache, drowsiness, dizziness,
Very rare	Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents, reports of poorly documented neuroleptic malignant syndrome
Eye disorders	
Rare	Difficulties in visual accommodation, blurred vision
Cardiac disorders	

Common	Tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase)
Rare	Angina pectoris
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Very common	Nausea, dry mouth
Common	Abdominal pain, vomiting (which may be alleviated by concomitant food intake), dyspepsia, toothache
Hepatobiliary disorders	
Very rare	Abnormal liver function, ranging from transaminase elevation to hepatic coma
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus, urticaria, fever, scalp hair loss, hyperhidrosis
Very rare	Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Uncommon	Trismus
Very rare	Muscle cramps
General disorders and administration site conditions	
Common	Feeling jittery
Rare	Slight growth retardation during prolonged use in children
Investigations	
Common	Weight decreased
Vascular disorders	
Common	Raynaud's phenomenon, peripheral coldness

[1] Includes angioneurotic oedema

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.

Adverse events reported since market introduction in patients taking methylphenidate include suicide, suicide attempt and suicidal ideation. No causal relationship between methylphenidate and these events has been established.

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

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

Table 7 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic disorders

pancytopenia

Psychiatric disorders

Dysphemia, suicidal ideation or attempt (including completed suicide), irritability, affect lability, abnormal thinking or behaviour, anger, altered mood, mood swings, hypervigilance, mania, disorientation, libido disorder[1], apathy, stereotypy[2], change in sustained attention[3], confusional state, drug abuse[4] and drug dependence

Nervous system disorders

Reversible ischemic 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

Erythema, fixed eruption[8]

Musculoskeletal, connective tissue and bone disorders

Myalgia, muscle twitching

Reproductive system and breast disorders

Priapism, erectile dysfunction, gynaecomastia

General disorders and administration site conditions

Chest pain, fatigue

Renal and urinary disorders

Enuresis

Investigations

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

Additional adverse reactions reported with other methylphenidate-containing products

The list below shows adverse reactions not listed for Ritalin that have been reported with other methylphenidate-containing products based on clinical trials data and post-market spontaneous reports.

Immune system disorders:	Hypersensitivity reactions such as auricular swelling
Renal and urinary disorders:	Haematuria, incontinence
General disorders and administration site conditions:	Sudden cardiac death
Investigations:	Cardiac murmur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Signs and symptoms of acute overdosage, mainly due to over-stimulation of the central nervous system and from excessive sympathomimetic effects, may include: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment

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

Treatment consists of appropriate 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 the Poisons Information Centre on 13 11 26 or current toxicological publication.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, further absorption may be limited by administration of activated charcoal. In cases of marked agitation, intravenous doses of diazepam or haloperidol should be given. Hypertension may be controlled by alpha-adrenergic blocking agents or intravenous sodium nitroprusside.

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

The efficacy of peritoneal dialysis or extracorporeal haemodialysis for methylphenidate overdosage has not been established. Clinical experience with overdose 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 infusion of calcium gluconate.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Pharmacotherapeutic group: psychostimulants.

ATC code: NO6B AO4.

5.1 PHARMACODYNAMICS

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

Mechanism of action

Methylphenidate is a central nervous system (CNS) stimulant. Its mode of action in humans is not completely understood but methylphenidate presumably exerts its stimulant effect by an inhibition of dopamine and norepinephrine reuptake into presynaptic neurons and thereby increasing these neurotransmitters in the extraneuronal space. There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioural effects in

children, nor conclusive evidence as to how these effects relate to the condition of the central nervous system.

The l-enantiomer is thought to be pharmacologically inactive.

Repeated oral administration of methylphenidate to young rats was associated with decreased spontaneous locomotor activity at systemic exposures (plasma AUC) about 3-fold that at the maximum clinical dose, due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females, at systemic exposures (plasma AUC) 8-fold that at the maximum clinical dose. The clinical relevance of these findings is unknown.

The effect of treatment with 40 mg dexmethylphenidate 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.

Clinical Trials

Studies in published literature have shown that Ritalin significantly improves daytime sleepiness and cataplexy.

ADHD in children

Ritalin LA was demonstrated to be effective in the treatment of ADHD in two placebo-controlled clinical studies in children aged 6 - 12 years with a DSM-IV diagnosis of ADHD (n = 195 exposed to study medicine).

The results of the first study (Protocol 02), a randomised, double-blind, placebo controlled, crossover clinical study conducted in a laboratory classroom setting, demonstrated that a single dose of 20 mg Ritalin LA had a rapid onset of effect and was statistically superior to placebo in improving classroom behaviour and cognitive responses. After administration of Ritalin LA, the improvement relative to placebo was statistically significant during both the morning (0 - 4 hours) and the afternoon (4 - 9 hours).

The second study (Protocol 07) was a randomised, double-blind, placebo controlled, parallel group clinical study conducted in normal school and home settings, in which Ritalin LA was administered once daily at individually titrated doses in the range of 10 - 40 mg/day for up to two weeks. The primary efficacy variable was the change from baseline to final score in the Connors ADHD/DSM-IV Scale for Teachers (CADS-T). CADS-T assesses symptoms of hyperactivity and inattention. The results of the analysis demonstrate that Ritalin LA was statistically superior to placebo ($p<0.0001$). The efficacy of Ritalin LA in controlling symptoms of ADHD was consistently reflected in the assessments of teachers, parents and investigators. The results of the primary efficacy analysis is summarised in Table 8.

Table 8: ADHD/DSM-IV Subscales for teachers and parents, change from baseline (ITT population, LOCF analysis)

	Ritalin LA		**Placebo**		
	n	Mean change[1] (SD[2])	n	Mean change[1] (SD[2])	p-value

	Ritalin LA		Placebo		
CADS-T subscale					
Total	62[3]	10.7 (15.7)	70[3]	-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

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

[2]standard deviation

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

ADHD in adults

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

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

Efficacy was assessed using the DSM-IV ADHD rating scale (DSM-IV ADHD RS) for symptomatic control and Sheehan Disability Score (SDS) for functional improvement as change in respective total scores from baseline to the end of the first period. All dose levels of Ritalin LA showed significantly greater symptom control ($p < 0.0001$ for all dose levels) compared to placebo as measured by a reduction in DSM-IV ADHD RS total score. All doses of Ritalin LA showed significantly greater functional improvement ($p = 0.0003$ at 40 mg, $p = 0.0176$ at 60 mg, $p < 0.0001$ at 80 mg) compared to placebo as measured by reduction in SDS total score (see Table 9).

Table 9: Analysis of improvement from baseline 1 to end of Period 1 in DSM IV ADHD RS total score and SDS total score by treatment / (LOCF*) for Period 1

		Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Change in DSM- IV ADHD RS from baseline	N	160	155	156	161
	LS mean*	15.45	14.71	16.36	9.35
	p- value	<0.0001	<0.0001	<0.0001	
	Significance level	0.0167	0.0208	0.0313	
Change in SDS total score from baseline	N	151	146	148	152
	LS mean	5.89	4.9	6.47	3.03
	p-value	0.0003	0.0176	<0.0001	
	Significance level***	0.0167	0.0208	0.0313	

* LOCF – Last Observation Carried Forward using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1

**LS mean- Least Square mean changes from Analysis of Covariance (ANCOVA) model with treatment group and center as factors and baseline DSM-IV ADHD RS total score and SDS total score as covariate

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

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

Maintenance of effect of Ritalin LA was evaluated by measuring the percentage of treatment failure in Ritalin LA compared to the placebo group at the end of a 6-month maintenance period (see Table 10). Completion rates varied across the treatment groups, with the lowest rate in the pacebo group (34.1%) and rates between 47.7% and 58.3% across the Ritalin LA dose group. Once the Ritalin LA dose was optimized in Period 2, approximately 79 % of patients continued to maintain disease control for a period of at least 6 months compared with approximately 50% given placebo ($p < 0.0001$ vs. placebo). An odds ratio of 0.3 suggested that patients treated with placebo had a 3 times higher chance of becoming a treatment failure compared to Ritalin LA.

Table 10: Percentage of treatment failures during Period 3

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

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

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

Patients who entered Period 3 had completed a total of between 5-14 weeks of Ritalin LA treatment in Periods 1 and 2. Patients then assigned to placebo in Period 3 did not experience increased signs of withdrawal and rebound compared to patients who continued on Ritalin LA treatment. The study performed in adults did not suggest any difference in efficacy or safety amongst gender subgroups (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

Efficacy was maintained or improved in the majority of subjects who elected to continue open-label treatment with Ritalin LA for up a further 26 weeks. Symptomatic improvement and a reduction in functional impairment was maintained or improved throughout the 26 week extension study period in the patients who elected to continue open label treatment with Ritalin LA.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ritalin 10 tablets

Following oral administration of Ritalin 10 tablets, the active substance, methylphenidate hydrochloride, is rapidly and almost completely absorbed from the tablets. 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 increased both the C_{max} (23%) and the AUC (15%) of methylphenidate, but had no effect on the rate of absorption. Peak plasma concentrations of approx. 40 nmol/litre (11 ng/mL) are attained, on the average, 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, is proportional to the size of the dose administered.

Ritalin LA capsules

Following oral administration of Ritalin LA capsules to children diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD) and adults, 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 capsules administered once daily is comparable to the same total dose of immediate release methylphenidate HCl tablets administered twice daily in children and in adults.

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for Ritalin LA capsules administered once daily compared to methylphenidate HCl tablets administered twice daily.

The mean pharmacokinetic parameters for Ritalin LA 40 mg capsules administered as a single dose once daily compared to methylphenidate HCl 20 mg immediate-release tablets administered twice daily four hours apart are summarised in Table 11.

Table 11: Mean pharmacokinetic parameters, geometric mean ratios and 90% CI for single dose Ritalin LA 40 mg capsules vs. IR MPH1 20 mg tablets twice daily four hours apart

	Ritalin LA (± SD[2])	**IR MPH[1] (± SD)**	**Geometric mean ratio (Ritalin LA/IR MPH)**	**90% CI**
C_{max1} (ng/mL)	14.0 (5.5)	13.2 (4.9)	1.03	0.90 - 1.18
C_{max2} (ng/mL)	17.0 (6.4)	19.5 (5.3)	0.82	0.75 - 0.90
Overall Cmax (ng/mL)	17.1 (6.2)	19.5 (5.4)	0.83	0.77 - 0.90
T_{max1} (h)	2.2 (1.1)	1.7 (0.5)	1.29	-[3]
T_{max2} (h)	5.8 (1.0)	5.7 (0.3)	1.02	-
AUC_{0-t} (ng.h/mL)	132 (48)	134 (41)	0.96	0.91 - 1.02
$AUC_{0-\infty}$ (ng.h/mL)	134 (49)	136 (43)	0.96	0.91 - 1.02

1 IR MPH = immediate release methylphenidate HCl tablets

2 SD = standard deviation

3 Not applicable

Food effects

Ritalin LA may be administered with or without food. There were no significant differences in AUC when Ritalin LA was administered with either a high fat breakfast or applesauce, compared to administration in the fasting condition, although a high fat meal and applesauce reduced C_{max2} by 25% and 13% respectively. 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 applesauce and administered (see 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Distribution

In the blood, methylphenidate and its metabolites become distributed in the plasma (57 %) and the erythrocytes (43 %). Methylphenidate and its metabolites have low plasma protein-binding (approximately 15 %). The apparent volume of distribution (Vd) has been calculated at 13.1 L/kg after an oral dose. The volume of distribution was 2.65 ± 1.11 L/kg for *d*-MPH and 1.80 ± 0.91 L/kg for *l*-MPH, following intravenous administration of 10 mg 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 (see 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Lactation). Adverse events were not noted in either infant (6 months and 11 months of age).

Metabolism

Biotransformation of methylphenidate, primarily by the carboxyl esterase CES1A1, is rapid and extensive. Peak plasma concentrations of the main, deesterified, metabolite, α-phenyl-2-piperidine acetic-acid (ritalinic acid), are attained about 2 hours after administration and are 30 to 50 times higher than those of the unchanged substance. The half-life of α-phenyl-2-piperidine acetic acid is about twice that of methylphenidate. 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.

Excretion Methylphenidate is eliminated from the plasma with a mean half-life of 2 to 3 hours, and the calculated mean systemic clearance is 4 to 10 L/h/kg after an oral dose. 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. Within 48 to 96 hours, 78 to 97% of the dose administered is excreted in the urine and 1 to 3% in the faeces in the form of metabolites. Unchanged methylphenidate appears in the urine only in small quantities (<1%). Most of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (60-86%).

Special populations

Effect of age

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

Patients with renal impairment

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

5.3 PRECLINICAL SAFETY DATA

Fertility

Methyphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18 week Continuous Breeding study. The study was conducted

at doses up to 160 mg/kg/day, approximately 11-fold the highest recommended human dose of methylphenidate on a mg/m^2 basis.

Reproductive animal toxicity

Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. Oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects at systemic exposures (plasma AUC) approximately 3 times clinical exposure at the maximum recommended human dose. The exposure at the no-effect dose was less than human exposure. In rats, teratogenic effects were not seen at systemic exposures (plasma AUC) approximately 12 times clinical exposure at the maximum recommended human dose.

Genotoxicity

Methylphenidate was not mutagenic in assays *in vitro* (Ames reverse mutation assay and the mouse lymphoma cell forward mutation assay). Methylphenidate showed evidence of a weak clastogenic response *in vitro* (Chinese Hamster Ovary cells) but was negative *in vivo* (mouse bone marrow micronucleus assay).

Carcinogenicity

In a lifetime carcinogenicity study carried out in B6C3F$_1$ mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumour type. The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumours in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 50 mg/kg/day, which is approximately 7 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis.

In a 24-week carcinogenicity study in the transgenic mouse strain p53$^{+/-}$, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; approximately 60 and 74 mg/kg/day of methylphenidate, respectively, which is approximately 4 and 5 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis, respectively.

Comment: The US Food and Drug Administration examined data from the Surveillance, Epidemiology and End Results (SEER) database for the years 1973 to 1991 and found that the estimated incidence of hepatoblastoma in the general population was not greater than 1 in 10 million person-years.

A total of 174 cases of hepatoblastoma were reported by the SEER for the period 1973 to 1995. The age-adjusted incidence rate is very low (IR=0.0382 per 100,000 person-years). The majority of cases (149 out of 174) were diagnosed among the age group 0 to 4 years old, which is in accordance with the natural history of the disease. For the age group 5 to 24 years old the rates of hepatoblastoma are very low with 14 cases reported. For the 0 to 4 years old age group, incidence rates of hepatoblastoma have risen slowly, ranging from 0.3032 per 100,000 in 1973 to 0.4889 per 100,000 in 1995. On the basis of

experience since marketing Ritalin 10, there is no evidence that the incidence is higher in patients receiving Ritalin 10.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ritalin 10 tablet lactose, calcium phosphate, gelatin, magnesium stearate, purified talc and wheat starch.

Ritalin LA capsules sugar spheres (sucrose and maize starch), methacrylic acid copolymer, purified talc, triethyl citrate, macrogol 6000, gelatin, titanium dioxide, iron oxide yellow CI77492 (10, 30, 40 mg and 60 mg capsules only), iron oxide black CI77499 (10, 40 mg and 60 mg capsules only), iron oxide red CI77491 (40 mg and 60 mg capsules only) and TekPrint SW-8010.

6.2 INCOMPATIBLITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Ritalin 10 tablets: Store below 25ºC. Protect from moisture.

Ritalin LA capsules: Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Ritalin 10: Blister packs
Ritalin LA: Bottles.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

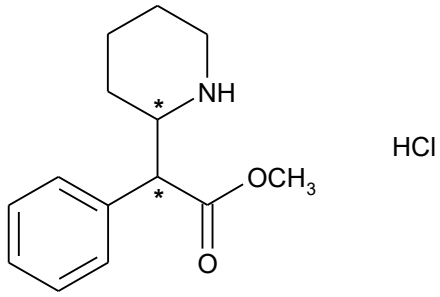
Chemical structure

Active ingredient: Methylphenidate hydrochloride

Chemical names: Methyl (R*, R*)-(±)-α-phenyl-2-piperidine acetate hydrochloride; or
2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride; or
Methyl α-phenyl-2-piperidineacetate hydrochloride

Molecular formula: $C_{14}H_{19}NO_2$. HCl

Molecular weight: 269.8



CAS Number

298-59-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug (S8).

8. NAME AND ADDRESS OF SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

Level 25, Victoria Cross Tower

155 Miller Street

North Sydney NSW 2060

Telephone: 1 800 671 203

Website: www.novartis.com.au

9. DATE OF FIRST APPROVAL

2 Aug 1991: AUST R 11052 RITALIN 10 methylphenidate hydrochloride 10mg tablet blister pack

21 Aug 2002: AUST R 82957, 82958, and 82959 RITALIN LA methylphenidate hydrochloride 20mg, 30 mg, and 40 mg capsule bottles

18 Dec 2009: AUST R 160228 RITALIN LA methylphenidate hydrochloride 10mg capsule Bottle

11 Mar 2016: AUST R 236251 RITALIN LA methylphenidate hydrochloride 60 mg capsule bottle

10. DATE OF REVISION

23 July 2026

® = Registered Trademark

Summary Table of Changes

Section	Summary of new information

1, 2, 3, 4, 5, 6, 7 ,8 , 9, 10	Editorial Change: Alignment of Bookmark Headings.
4.4	Addition of general precaution stimulant warning
8	Update to sponsor address and contact information

Internal Document Code

Rtl230726i based on CDSv4.1 dated 20 March 2026