**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.

**NAME OF THE DRUG**

Ritalin 10 tablets and Ritalin LA capsules contain the active ingredient, methylphenidate, as the hydrochloride salt.

Methylphenidate hydrochloride is a white, finely crystalline, odourless powder; freely soluble in water and methanol, soluble in ethanol and slightly soluble in chloroform and acetone. It is a racemic mixture comprised of the \(d\)- and \(l\)-threo enantiomers.

Chemical name: Methyl (R*, R*)-(±)-\(\alpha\)-phenyl-2-piperidine acetate hydrochloride

Molecular formula: \(C_{14}H_{19}NO_2 \cdot HCl\)

Molecular weight: 269.8

CAS number: 298-59-9

**DESCRIPTION**

**Ritalin 10 tablets**

One tablet of Ritalin 10 contains 10 mg of methylphenidate hydrochloride.

**Excipients**: lactose, calcium phosphate, gelatin, magnesium stearate, purified talc and wheat starch.

**Ritalin LA capsules**

One modified-release capsule of Ritalin LA contains 10 mg, 20 mg, 30 mg or 40 mg of methylphenidate hydrochloride. Each capsule contains half the dose as immediate release beads and the remaining half of the dose as enteric-coated, delayed-release beads. Thus providing an immediate release of methylphenidate followed by a delayed release of methylphenidate.

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

**PHARMACOLOGY**

**Pharmacodynamics**

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

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 reuptake in the striatum, without triggering the release of dopamine. 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.

**Pharmacokinetics**

**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 $C_{\text{max}}$ (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, are 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.

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 1.
Table 1  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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ritalin LA (± SD)</th>
<th>IR MPH1 (± SD)</th>
<th>Geometric mean ratio (Ritalin LA/IR MPH)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax1 (ng/mL)</td>
<td>14.0 (5.5)</td>
<td>13.2 (4.9)</td>
<td>1.03</td>
<td>0.90 - 1.18</td>
</tr>
<tr>
<td>Cmax2 (ng/mL)</td>
<td>17.0 (6.4)</td>
<td>19.5 (5.3)</td>
<td>0.82</td>
<td>0.75 - 0.90</td>
</tr>
<tr>
<td>Overall Cmax (ng/mL)</td>
<td>17.1 (6.2)</td>
<td>19.5 (5.4)</td>
<td>0.83</td>
<td>0.77 - 0.90</td>
</tr>
<tr>
<td>Tmax1 (h)</td>
<td>2.2 (1.1)</td>
<td>1.7 (0.5)</td>
<td>1.29</td>
<td>^3</td>
</tr>
<tr>
<td>Tmax2 (h)</td>
<td>5.8 (1.0)</td>
<td>5.7 (0.3)</td>
<td>1.02</td>
<td>^3</td>
</tr>
<tr>
<td>AUC(0-t) (ng.h/mL)</td>
<td>132 (48)</td>
<td>134 (41)</td>
<td>0.96</td>
<td>0.91 - 1.02</td>
</tr>
<tr>
<td>AUC(0-x) (ng.h/mL)</td>
<td>134 (49)</td>
<td>136 (43)</td>
<td>0.96</td>
<td>0.91 - 1.02</td>
</tr>
</tbody>
</table>

1 IR MPH = immediate release methylphenidate HCl tablets
2 SD = standard deviation
3 Not applicable

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 $C_{\text{max}2}$ 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 DOSAGE AND 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 (see PRECAUTIONS – Use in Lactation).

Metabolism:

Methylphenidate is primarily metabolised by the carboxylesterase CES1A1. Peak plasma concentrations of the main, deesterified, metabolite - $\alpha$-phenyl-2-piperidine acetic-acid (ritalinic acid) - are attained about 2 hours after administration and are 30 to 50 times higher than those of the unchanged substance. The half-life of $\alpha$-phenyl-2-piperidine acetic acid is about twice that of methylphenidate.

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%). The bulk of the dose is excreted in the urine as \(\alpha\)-phenyl-2-piperidine acetic acid (60-86%).

**Characteristics in patients:**
There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and normal adults.

**CLINICAL TRIALS**

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 total subscale for teachers (CADS-T). 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.

**INDICATIONS**

**Attention-Deficit Hyperactivity Disorder (ADHD)**

*Ritalin 10 tablets and Ritalin LA capsules are indicated for the treatment of 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 part of a comprehensive treatment programme which typically includes other remedial measures (psychological, educational, social) for achieving a beneficial effect in children with a behavioural syndrome characterised by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity (not always present) and impulsivity. The diagnosis of this syndrome should not be made when these symptoms are only of recent origin. Non-localising (soft) neurological signs, emotional lability, learning disability and an abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

**Special diagnostic considerations for ADHD:**

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.

**Narcolepsy**

*Ritalin 10 tablets are also indicated for the treatment of 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.

**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 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.

**PRECAUTIONS**

**Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems**

**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. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products, including methylphenidate, generally should not be used in children or adolescents 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 DOSAGE AND 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.

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

**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 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 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 elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with Ritalin (see PRECAUTIONS – Cardiovascular Conditions).
**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 DOSAGE AND ADMINISTRATION).

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

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 ADVERSE 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:**

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Ritalin. However patients with ADHD may experience aggression as part of their medical condition. Therefore, causal association with treatment is difficult to assess. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

**Suicidal tendency:**

Patients with emergent suicidal ideation and behaviour during treatment for ADHD should be evaluated immediately by their physician. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

**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 ADVERSE REACTIONS). 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 children should precede use of methylphenidate for ADHD treatment. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.
Other

Use in children:
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.

Long term suppression of growth
Moderately reduced weight gain and slight growth retardation have been reported with the long term use of stimulants, including methylphenidate, in children. 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 "ADVERSE REACTIONS" 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.

Drug dependence:
Ritalin should be given cautiously to patients with a history of drug or alcohol dependence. Chronic abuse can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. 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.

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

Chronic abuse of methylphenidate can lead to marked tolerance and psychic dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially in
response to parenteral abuse. Methylphenidate abuse or dependence does not appear to be a problem in adolescents or adults who were treated with methylphenidate for ADHD as children.

Careful supervision is required during drug withdrawal, since depression as well as the effects of chronic over-activity can be unmasked. Long-term follow-up may be needed for some patients.

**Treatment considerations:**
Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only in the light of the complete history and evaluation of the child. The decision to prescribe methylphenidate should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness to his or her 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.

**Long term use:**
Data on safety and efficacy of long-term use of methylphenidate are not complete. Therefore, patients requiring long-term therapy should be carefully monitored.

**Laboratory measurements:**
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 ADVERSE EFFECTS)

**Effects on ability to drive and use machines:**
Ritalin may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see ADVERSE EFFECTS). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

**Carcinogenicity**
In a lifetime carcinogenicity study carried out in B6C3F1 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/m² 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/m² 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/m² 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.

**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).

**Effects on fertility**
Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 11-fold the highest recommended human dose of methylphenidate on a mg/m² basis.

**Use in Pregnancy (Category B3)**
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.

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.

There are no adequate and well-controlled studies in pregnant women. Therefore, until more information is available, methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

**Use in Lactation**
Case reports showed that methylphenidate was distributed into breast milk. 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.

**INTERACTIONS WITH OTHER DRUGS**

**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 PRECAUTIONS - 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 CONTRAINDICATIONS).

**Use with halogenated anaesthetics:**
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, Ritalin should not be taken on the day of surgery.

**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). The coadministration of Ritalin with antipsychotics is not recommended because of the counteracting mechanism of action.

**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.

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

**ADVERSE EFFECTS**

**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. Decreased appetite is also common but usually transient.

In children, loss of appetite, abdominal pain, insomnia and tachycardia may occur more frequently. However, any of the other adverse reactions listed below may also occur.
Adverse reactions listed below are ranked under headings of frequency, using the following convention: very common $\geq 10\%$; common $\geq 1\%$ to $<10\%$; uncommon $\geq 0.1\%$ to $<1\%$; rare $\geq 0.01\%$ to $<0.1\%$; very rare $<0.01\%$.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse reactions reported with Ritalin/Ritalin LA use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Leucopenia, thrombocytopenia, anaemia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Hypersensitivity reaction, including angioedema and anaphylaxis</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Rare</td>
<td>Moderately reduced weight gain during prolonged use in children</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Nervousness, insomnia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Nervousness, insomnia, irritability</td>
</tr>
<tr>
<td>Common</td>
<td>Headache, drowsiness, dizziness, dyskinesia</td>
</tr>
<tr>
<td>Very rare</td>
<td>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</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Difficulties in visual accommodation, blurred vision</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Tachycardia, palpitation, arrhythrias, changes in blood pressure and heart rate (usually an increase)</td>
</tr>
<tr>
<td>Rare</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Decreased appetite, abdominal pain, nausea, vomiting (which may be alleviated by concomitant food intake), dry mouth</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Abnormal liver function, ranging from transaminase elevation to hepatic coma</td>
</tr>
</tbody>
</table>
Skin and subcutaneous tissue disorders

Common Rash, pruritus, urticaria, fever, scalp hair loss

Very rare Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme

Musculoskeletal and connective tissue disorders

Common Arthralgia

Very rare Muscle cramps

General disorders and administration site conditions

Rare Slight growth retardation during prolonged use in children

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.

Clinical Trial with Ritalin LA

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 3.

Table 3 Treatment-emergent adverse events¹ with an incidence of ≥2% in the two-week double-blind treatment phase of a placebo controlled clinical study of Ritalin LA (Protocol 07)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ritalin LA N = 65 (%)</th>
<th>Placebo N = 71 (%)</th>
<th>Adverse event</th>
<th>Ritalin LA N = 65 (%)</th>
<th>Placebo N = 71 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16 (24.6)</td>
<td>17 (23.9)</td>
<td>Headache</td>
<td>1 (1.5)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (3.1)</td>
<td>0 (0.0)</td>
<td>Sore throat</td>
<td>0 (0.0)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (3.1)</td>
<td>0 (0.0)</td>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

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.

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 4.
### Table 4  Adverse events with an incidence ≥2% in all treated subjects in Protocol 07

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ritalin LA N = 161</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Total</td>
<td>103 (64.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (16.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (10.6)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Appetite, decreased</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Irritability</td>
<td>8 (5.0)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8 (5.0)</td>
</tr>
<tr>
<td>URTI</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (2.5)</td>
</tr>
</tbody>
</table>

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.

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

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

- **Infections and infestations:** Nasopharyngitis
- **Blood and lymphatic disorders:** Pancytopenia
- **Immune system disorders:** Hypersensitivity reactions such as auricular swelling
- **Psychiatric disorders:** Anxiety, irritability, aggression, affect lability, agitation, abnormal behaviour or thinking, anger, suicidal ideation or attempt (including completed suicide), mood altered, mood swings, hypervigilance, mania, disorientation, libido disorder, apathy, repetitive behaviours, over-focussing, confusional state, dependence, cases of abuse and dependence have been described, more often with immediate release formulations
- **Nervous system disorders:** Tremor, reversible ischaemic neurological deficit, migraine
- **Eye disorders:** Diplopia, Mydriasis, visual disturbance
- **Cardiac disorders:** Cardiac arrest, myocardial infarction
- **Vascular disorders:** Peripheral coldness, Raynaud's phenomenon
- **Respiratory, thoracic and mediastinal disorders:** Cough, pharyngolaryngeal pain, dyspnoea
- **Gastrointestinal disorders:** Diarrhoea, constipation
Skin and subcutaneous tissue disorders: Angioneurotic oedema, hyperhidrosis, erythema, fixed drug eruption

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

Renal and urinary disorders: Haematuria

Reproductive system and breast disorders: Gynaecomastia

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

Investigations: Weight decreased, cardiac murmur

**DOSAGE AND ADMINISTRATION**

Treatment should only be initiated by specialist physicians with experience in the use of the drug.

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. Daily dosage should not exceed 60 mg. 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 a one-month period, the drug should be discontinued.

Ritalin 10/ Ritalin LA should be discontinued periodically (e.g. over weekends, school holidays and long vacation) to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued. Drug treatment should not, and need not, be indefinite and usually may 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.

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 (see CONTRAINDICATIONS and PRECAUTIONS).

**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 1-2 hours before the maximum effect is required.
**Children (6 years and over):**

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.

**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 to 60 mg daily. In others, 10 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.

**Ritalin LA capsules**

Ritalin LA capsules should be administered orally once daily in the morning. The recommended starting dose of Ritalin LA is 20 mg. The capsules may be administered with or without food. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with Ritalin LA 10 mg. 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 may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of soft food. In that case, the capsules may be carefully opened and the beads sprinkled 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.

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

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.

The recommended single daily dose of Ritalin LA for patients currently taking Ritalin 10 tablets twice daily is provided below:

<table>
<thead>
<tr>
<th>Previous dose of Ritalin 10 tablets</th>
<th>Recommended dose of Ritalin LA capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg twice daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>10 mg twice daily</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>15 mg twice daily</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>20 mg twice daily</td>
<td>40 mg daily</td>
</tr>
</tbody>
</table>

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.
OVERDOSAGE

Symptoms
Signs and symptoms of acute overdosage, resulting principally from over-stimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: 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 and dryness of mucous membranes.

Treatment
When treating 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 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.

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

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentations
Ritalin 10 tablets: Blister pack containing 100 tablets.
- 10 mg: white, scored, marked AB, CG on reverse.

Ritalin LA capsules: Bottles containing 30 or 100* capsules.
- 10 mg: white to off-white beads in a light brown opaque hard gelatin capsule with imprint NVR on cap and R10 on a white opaque body in tan-coloured ink.
- 20 mg: white to off-white beads in a white opaque hard gelatin capsule with imprint NVR on cap and R20 on body in tan-coloured ink.
- 30 mg: white to off-white beads in a yellow opaque hard gelatin capsule with imprint NVR on cap and R30 on body in tan-coloured ink.
- 40 mg: white to off-white beads in a light brown opaque hard gelatin capsule with imprint NVR on cap and R40 on body in tan-coloured ink.

* Some presentations may not be available

Storage
Ritalin 10 tablets: Store below 25°C. Protect from moisture.
Ritalin LA capsules: Store below 30°C.
POISONS SCHEDULE

Controlled Drug (S8)

NAME AND ADDRESS OF SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113
® = Registered Trademark

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

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

APPROVED BY THERAPEUTIC GOODS ADMINISTRATION

14 December 2009

DATE OF MOST RECENT AMENDMENT

24 August 2012