Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ritalin LA 40mg prolonged-release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prolonged-release capsules containing 40 mg, methylphenidate hydrochloride.

Excipients with a known effect: each hard capsule contains 225.89 of sucrose

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsules, hard.

White to off-white beads in a light brown opaque hard gelatine capsule, size 1, with imprint NVR (cap) and R40 (body) in tan-coloured ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)
Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient.

Ritalin LA is indicated in the treatment of ADHD in adults as part of a comprehensive treatment programme.

Special Diagnostic Considerations for ADHD in children
Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM criteria or the guidelines in ICD and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

Special Diagnostic Considerations for ADHD in adults
Treatment must be initiated and be under the supervision of a specialist in treatment of behavioural disorders. Diagnosis should be made according to DSM criteria or the guidelines in ICD and should be based on a complete history and evaluation of the patient.

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adults with ADHD have symptom patterns characterized by, restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD. Diagnosis in adults should include a structured patient interview to determine current symptoms. The preexistence of childhood ADHD is required and has to be determined retrospectively (by patients' records or if not available by appropriate and structured instruments/interviews). Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment and diagnosis should include moderate or severe functional impairment in at least 2 settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

4.2 Posology and method of administration

In children, treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders. In adults treatment must be initiated under the supervision of a specialist in treatment of behavioural disorders.

Pre-treatment screening
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and, in children, accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4).

Ongoing monitoring:
Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- height, weight and appetite should be recorded in children at least 6 monthly with maintenance of a growth chart;
- weight should be recorded in adults regularly;
- development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration in children should be started at the lowest possible dose. Dose titration in adults can be started at 20mg.
Other strengths of this medicinal product and other methylphenidate-containing products may be available.
If symptoms do not improve after dose titration over a period of one month, the drug should be discontinued.
If symptoms worsen or other adverse effects occur, the dosage should be reduced or, if necessary, the drug discontinued.
The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.
Long acting Ritalin capsules should not be taken too late in the morning as it may cause disturbances in sleep.

Children (6 years and over)
Ritalin LA capsules are for oral administration once daily in the morning. The recommended starting dose is 1 capsule Ritalin 20 mg. When in the judgment of the clinician a lower initial dose is appropriate, the patient may begin treatment with Ritalin LA capsules 10 mg, alternatively it is recommended to start with conventional short acting Ritalin 10 mg tablet and continuously increase according to the recommendation for this formulation. The maximum daily dosage of methylphenidate is 60mg.
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 the standard Ritalin tablet may help to solve this problem.
In that case, it could be considered that adequate symptom control might be achieved with a twice daily short acting Ritalin 10 mg tablet regimen.
The pros and cons of a small evening dose of a short acting Ritalin 10 mg tablet versus disturbances in falling asleep should be considered.
Treatment should not continue with long acting Ritalin capsules if an additional late dose of a short acting Ritalin 10 mg tablet is required, unless it is known that the same extra dose was also required for a conventional immediate-release regimen at equivalent breakfast/lunchtime dose.

Adults
Ritalin LA is for oral administration once daily usually in the morning. The time of the intake may be adapted according to the patient's individual needs, but intake should not be too late in order to prevent sleep disturbances.
The dose should be titrated individually. The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.
Only the Ritalin LA formulation should be used for the treatment of ADHD in adults. A maximum daily dose of 80 mg should not be exceeded.

Patients new to methylphenidate (see section 5.1): The recommended starting dose of Ritalin LA in patients who are not currently taking methylphenidate is 20 mg once daily. Ritalin LA dosage may be adjusted at weekly intervals in 20 mg increments for adults.

Patients transitioning from childhood Ritalin treatment to adulthood: Treatment may be continued with the same daily dose. If the patient was previously treated with an immediate release formulation, a conversion to an appropriate recommended dose of Ritalin LA should be made (see below subsection "Switching patient's treatment to Ritalin LA")

Periodic assessment of the treatment in ADHD
Ritalin LA should be discontinued periodically to assess the patient's condition. Improvement may continue when the drug is temporarily or permanently discontinued. Treatment may be restarted as appropriate to control the symptoms of ADHD. Drug treatment should not, and need not, be indefinite. When used in children with ADHD, treatment can usually be discontinued during or after puberty.

Method of administration
Ritalin LA (methylphenidate hydrochloride prolonged-release capsules) is for oral administration once daily in the morning. Ritalin LA capsules may be administered with or without food. They may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of food (see specific instructions below).
Ritalin LA capsules and/or their contents should not be crushed, chewed, or divided.

Administration by sprinkling capsule contents on food
The capsules may be carefully opened and the beads sprinkled over soft food (e.g. apple sauce). The food should not be warm because this could affect the prolonged-release properties of this formulation. The mixture of drug and food should be consumed immediately in its entirety. The drug and food mixture should not be stored for future use.

Switching patient's treatment to Ritalin LA
Ritalin LA, administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of Ritalin administered b.i.d.
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 are provided in table 1.

Table 1

Previous methylphenidate dose	Recommended Ritalin LA dose
10 mg methylphenidate b.i.d	20 mg qd (per day)
15 mg methylphenidate b.i.d	30 mg qd (per day)
20 mg methylphenidate b.i.d	40 mg qd (per day)

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose.

The maximum daily dosage of methylphenidate is 60mg for treatment of ADHD in children, and 80mg for treatment of ADHD in adults.

Long-term (more than 12 months) use
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled clinical trials in children and adolescents. The long term safety of methylphenidate has not been systematically evaluated in controlled clinical trials in adults. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in patients with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate

is de-challenged at least once yearly to assess the patient's condition (for children, preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation
Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Adults
Methylphenidate Ritalin LA only is licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group for other Ritalin formulations.

Elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group. Ritalin LA has not been studied in ADHD in patients older than 60 years.

Children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Hepatic impairment
Ritalin has not been studied in patients with hepatic impairment. Caution should be exercised in these patients.

Renal impairment
Ritalin has not been studied in patients with renal impairment. Caution should be exercised in these patients.

4.3 Contraindications

Known sensitivity to methylphenidate or any of the excipients

- Glaucoma
- Phaeochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Long-term use (more than 12 months)
The long term safety of methylphenidate has not been systematically evaluated in controlled clinical trials in adults. The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials in children and adolescents. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in the elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group. Ritalin LA has not been studied in ADHD in patients older than 60 years.

Use in children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia,) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls.

Changes in diastolic and systolic blood pressure values were also observed in clinical trial data from adults ADHD patients. However these changes were smaller compared to children and adolescents (around 2-3 mmHg relative to controls). The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which methylphenidate treatment in contraindicated. See section 5.1 under subheading "ADHD in adults".

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders unless specialist cardiac advice has been obtained (see Section 4.3 'Contraindications').

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in patients with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

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

Cerebrovascular disorders
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment in contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an

underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing Psychotic or manic symptoms
In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in patients without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension
Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 month or every visit.

Forms of bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Growth
Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. Weight decrease has been reported with Ritalin LA treatment in adults.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored in children during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. In adults weight should be regularly monitored.

Seizures
Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Abuse, misuse and diversion
Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate.

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD.

Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

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

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

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

Excipients: Sugar spheres (Sucrose)
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Choice of methylphenidate formulation
The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect. For the treatment of ADHD in adults, only the Ritalin LA formulation should be used.

Drug screening
This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency
There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with methylphenidate is not fully known. In the event of Leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Priapism
Prolonged and painful erections have been reported in association with methylphenidate products, mainly in association with a change in the methylphenidate treatment regimen. Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

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

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbitol, phenytoin, primodone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive drugs
Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4 Warnings and Precautions for use)
Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3 Contraindications).

Use with alcohol
Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.
In case of very high alcohol concentrations the kinetic profile may change towards a more immediate release-like pattern.

Use with halogenated anaesthetics
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used 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. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with domapinergic drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses. (See section 5.3).

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Lactation
Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate.
There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of methylphenidate on fertility are available. In animal studies, no clinically relevant effects on fertility were observed**.**

4.7 Effects on ability to drive and use machines

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with Ritalin LA and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with Ritalin LA and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:

- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1000 to <1/100)
- rare (≥ 1/10,000 to <1/1000)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data).

Infections and infestations
Common: Nasopharyngitis
Uncommon: Gastroenteritis

Blood and lymphatic disorders
Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
Not known: Pancytopenia

Immune system disorders
Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders*
Very common: decreased appetite
Common: anorexia, moderately reduced weight and height gain during prolonged use in children

Psychiatric disorders*
Very common: insomnia, nervousness
Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour, restlessness, sleep disorder, libido decreased, panic attack, stress, bruxism**
Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome, hypervigilance, tension
Rare: mania*, disorientation, libido disorder
Very rare: suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focussing,
Not known: delusions*, thought disturbances*, confusional state, dependence, logorrhea.
Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

Nervous system disorders
Very common: headache
Common: tremor, dizziness, dyskinesia, psychomotor hyperactivity, somnolence
Uncommon: sedation, Akathisia
Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit Neuroleptic malignant syndrome (NMS; Reports were poorly documents and in most of cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).
Not known: cerebrovascular disorders*(including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine, dysphemia

Eye disorders
Uncommon: diplopia, blurred vision,
Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*
Common: arrhythmia, tachycardia palpitations
Uncommon: chest pain
Rare: angina pectoris
Very rare: cardiac arrest, myocardial infarction
Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*
Common: hypertension, peripheral coldness
Uncommon:
Very rare: cerebral arteritis and/or occlusion, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Common: cough, pharyngolaryngeal pain, dysponea
Not known: epistaxis

Gastrointestinal disorders
Very common: nausea, dry mouth.
Common: abdominal pain, diarrhoea, stomach discomfort, and vomiting, dyspepsia, toothache.
Uncommon: constipation

Hepatobiliary disorders
Uncommon: hepatic enzyme elevations
Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders
Common: hyperhidrosis, alopecia, pruritus, rash, urticaria
Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions
Rare: macular rash, erythema
Very rare: erythema multiforme, exfoliative dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia
Uncommon: myalgia, muscle twitching, muscle tightness
Very rare: muscle cramps
Not known: Trismus**

Renal and urinary disorders
Uncommon: haematuria
Not known: incontinence

Reproductive system and breast disorders
Rare: Gynaecomastia

Not known: Priapism, erection increased and prolonged erection

General disorders and administration site conditions
Common: pyrexia, growth retardation during prolonged use in children*, feeling jittery, fatigue, thirst
Uncommon: chest pain,
Very rare: sudden cardiac death*
Not known: chest discomfort, hyperpyrexia

Investigations
Common: changes in blood pressure and heart rate (usually an increase)weight decreased
Uncommon: cardiac murmur, hepatic enzyme increased
Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

* See Section 4.4 'Special warnings and precautions for use'
** Based on the frequency calculated in adult ADHD studies no cases were reported in the paediatric Studies

ADRs from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents
ADRs from clinical trials in adult patients that were not reported in children and adolescents

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from this formulation.

Signs and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes and rhabdomyolysis.

Treatment

There is no specific antidote to methylphenidate overdosage.
Treatment consists of appropriate supportive measures.
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, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine be given before performing gastric lavage.
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 overdose of methylphenidate has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychostimulants (ATC code NO6B AO4).

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

Mode of Action

Ritalin LA is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood but its stimulant effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.
The mechanism by which Ritalin LA exerts its mental and behavioural effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system.
The l-enantiomer is thought to be pharmacologically inactive. The d isomer is pharmacologically more active than the l isomer.

ADHD in adults

Ritalin LA was evaluated in a combined short-term and long-term core study consisting of three periods (Period 1= 9 weeks short-term treatment, Period 2= 5 weeks open label treatment with Ritalin LA without placebo control; Period 3= randomised withdrawal phase). This core study was followed by a 26-week open label extension study.

This The core study was 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 efficacy and safety of Ritalin LA in 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 improvement 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 improvement in SDS total score (see Table 2).

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 in favor of Ritalin LA over placebo across all assessments in period 1.

Table 1 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
Improvement 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	
Improvement 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 improvement 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 ****p-value refer to comparison against placebo

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 3). 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 (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 2 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.

During short-term treatment both females and males had a statistically better improvement of DSM-IV ADHD RS compared to placebo in all Ritalin dose groups. For men best numerical improvement of the score was achieved with Ritalin LA 80 mg, whereas for women best improvement was reached in the lowest does group Ritalin LA 40 mg. This trend was not significant, and not seen during long-term treatment. A slightly higher incidence of AEs was observed in females compared to males; however, in general, a similar safety profile was demonstrated for males and females. Therefore the dose should be titrated individually (maximal possible dose 80 mg/d). The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

The 26-week open label extension of the core study of Ritalin LA in 298 adult patients with ADHD showed long term safety of Ritalin LA. Combining the continuous exposure to Ritalin LA of all patients treated in the core and the extension studies, a total of 354 patients continuously received Ritalin LA for > 6 months and 136 patients for > 12 months.

The safety profile of Ritalin LA did not change with the longer duration of treatment of adult ADHD patients, as observed during this extension study. The AE profile seen in the extension patients was similar to that observed in the core study. No unexpected SAEs were observed in this extension study and also most of the observed AEs were expected.

Nevertheless the total frequency of AE and some specific AE increased with exposure time. Decreased weight occurred in 0.7% (≤ 2 months), 5.6% (> 6 months) and 7.4% (> 12 months) of the patients. In period 3 there was a significant weight decrease ≥ 7% in 13.8% of the patients in Period 3 (in the 6-months maintenance period) compared to baseline. Insomnia/initial insomnia/sleep disorder increased with long-term treatment > 12 months. Incidence of depressed mood slightly increased over time (4.8% for the periods of <2 months, 4.5% for >6 months and 6.6% >12 months) whereas depression decreased over time (0% in > 12 months). Incidence of tachycardia and palpitations slightly increased with long-term exposure (tachycardia: 4.8% with exposure < 2 months and 6.6% with exposure > 12 months; palpitations 6.9% with exposure < 2 months and 9.6% with exposure > 12 months). Also incidence of high blood pressure slightly increased with long-term exposure; from 2.1% with exposure < 2 months to 5.1% with exposure > 12 months. Mean change in HR increased from 2.4 bpm (exposure < 2 months) to 4.9 resp. 4.8 bpm (exposure > 6 months resp. exposure > 12 months).

Tachycardia: At baseline, the percentage of patients with a heart rate > 100 bpm was very small (0.4% in the All Ritalin LA group and 0.6% in the placebo group). Whereas with Ritalin LA 11.3% of those with a normal baseline heart rate developed a heart rate > 100 bpm in at least one of the visits during short-term treatment (and only 2.2% in the placebo group).

During long-term treatment 8.6% compared to 3.4% (Ritalin LA vs. placebo) of those with a normal baseline heart rate developed a heart rate > 100 bpm in at least one of the visits.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of Ritalin LA® (prolonged-release capsules) to children diagnosed with ADHD and adults, methylphenidate is rapidly absorbed and produces a bi-modal plasma concentration-time profile (i.e. two distinct peaks approximately four hours apart). The relative bioavailability of Ritalin LA® given once daily is comparable to the same total dose of Ritalin® or methylphenidate tablets given twice a day in children.
The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for Ritalin® LA given once a day compared to Ritalin® tablets given twice a day.

Food Effects
Ritalin® LA may be administered with or without food. There were no differences in the bioavailability of Ritalin® LA when administered with either a high fat breakfast or applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.
For patients unable to swallow the capsule, the contents may be sprinkled on soft food such as applesauce and administered (see Posology and method of administration).

Distribution
In the blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%) Methylphenidate and its metabolites have a low plasma protein-binding (10-33%). The volume of distribution was 2.65±1.11 L/kg for d-MPH and 1.80±0.91 L/kg for l-MPH

Biotransformation
Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Peak plasma concentrations of μ-phenyl-2-piperidine acetic acid (ritalinic acid)are attained about 2 hours after administration and are 30-50 times higher than those of the unchanged substance. The half-life of α-phenyl-2-piperidine acetic acid is about twice that of methylphenidate, and its mean systemic clearance is 0.17 L/h/kg. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

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

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

Carcinogenicity
In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

Comment:
The US Food and Drugs 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. Age-adjusted incidence rate was very low (IR=0,0382 per 100,000 person-years). The majority of the 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 were very low with few or no cases reported.

On the basis of experience since marketing Ritalin®, there is no evidence that the incidence is higher in patients receiving Ritalin® LA.

Juvenile neurobehavioural development
Repeated oral administration of methylphenidate to young rats identified decreased spontaneous locomotor activity at 50 mg/kg/day (29-fold higher than the MRHD), due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females and at the highest dose of 100 mg/kg/day (58-fold higher than the MRHD). The clinical relevance of these findings is unknown.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonio methacrylate copolymer
Methacrylic acid-methyl methacrylate copolymer
Macrogol
Sugar spheres (containing sucrose and maize starch)
Talc

Triethyl citrate

Capsule shell
Gelatin
Titanium dioxide
Iron oxide yellow
Iron oxide black
Iron oxide red

Printed ink Tan SW-8010
Containing
Iron oxide red
Iron oxide yellow
Potassium hydroxide
Propylene glycol
Shellac
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottles containing 30 and 100 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

InfectoPharm Arzneimittel und Consilium GmbH
Von-Humboldt-Str. 1,
64646 Heppenheim
Germany

8 MARKETING AUTHORISATION NUMBER

PA1972/002/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th July 2003

Date of last renewal: 31st October 2009

10 DATE OF REVISION OF THE TEXT

September 2022