SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ritalin XL 20 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg methylphenidate hydrochloride.
Excipient(s) with known effect:
Each capsule contains 113 mg sucrose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

White, opaque, hard gelatin capsules, size 2, imprinted with “NVR” on the cap and “R20” on the body, containing white to off-white beads that are roughly spherical in shape.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-deficit hyperactivity disorder (ADHD)

Ritalin XL is indicated as a part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) in children and adolescents aged 6 years and over and in adults when remedial measures alone prove insufficient.

Treatment must be initiated and supervised by a doctor specialised in the treatment of ADHD such as an expert paediatrician, a child and adolescent psychiatrist or a psychiatrist.

Special diagnostic considerations for ADHD in children and adolescents

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 this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity and the 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 the way according to the licensed indication and according to the prescribing/diagnostics guidelines.

Special diagnostic considerations for ADHD in adults

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 aetiology of this syndrome is unknown, and there is no single diagnostic test. Adults with ADHD have symptom patterns characterised 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 pre-existence of childhood ADHD is required and has to be determined retrospectively by patients' records (e.g., medical records, school reports) or if not available by appropriate and structured instruments/interviews (e.g., WURS scale, questionnaires for family and friends).

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

Treatment must be initiated and supervised by a doctor specialised in the treatment of ADHD such as an expert paediatrician, a child and adolescent psychiatrist or a psychiatrist.

Formulation

The specific galenics of Ritalin XL imitates the twice-daily administration of an immediate-release methylphenidate formulation. The capsules contain an equal amount of two different types of beads (immediate- and delayed-release), yielding

50 % of the active substance in the non-retarded, immediate-release form, while the remaining 50 % are released after approximately 4 hours (see section 5.2).

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 or psychiatric disorders;
- In children, accurate recording of pre-treatment height and weight on a growth chart;
- In adults, accurate recording of body weight (see sections 4.3 and 4.4).

Ongoing monitoring

Patient growth (in children), weight, psychiatric and cardiovascular status should be continuously monitored (see 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;
- In children height, weight, and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- In adults, weight should be recorded regularly;
- Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

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

Posology

Dose titration

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest dose deemed appropriate for the individual patient, with small increments at weekly intervals until a tolerable and sufficiently effective dose is reached (see further details below in the respective sub-sections for *children and adolescents* and *adults*).

The dose should be determined according to the patient's age and severity of the symptoms, the clinical assessment and the patient's response and should be individualised according to the patient's needs. The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed. The effect occurs within an hour after ingestion if the dose is sufficiently high.

Ritalin XL capsules should not be taken too late in the day in order to prevent sleep disturbances.

In the treatment of ADHD, an attempt should be made to time administration to coincide with the periods of greatest academic/professional, behavioural, or social stress.

Other strengths of this medicinal product and other methylphenidate containing products may be available.

Paediatric population

Children and adolescents (6 years of age and over)

Ritalin XL capsules are for oral administration once daily in the morning.

In general, using a conventional immediate-release formulation, the recommended starting dose of methylphenidate is 5 mg once or twice daily (e.g., half a Ritalin 10 mg tablet, in the morning and at lunchtime). The dose may be increased, if necessary, by weekly increments of 5-10 mg in the daily dose.

Alternatively, when the treating physician considers that 10 mg is the appropriate daily starting dose, Ritalin XL 10 mg capsules once daily can be used from the beginning of treatment in place of immediate-release methylphenidate 5 mg twice daily. When, in the judgment of the clinician, a higher initial dose is appropriate, the patient may begin treatment with Ritalin XL 20 mg capsules.

The maximum daily dose of methylphenidate in children and adolescents is 60 mg.

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 an immediate-release (short-acting) methylphenidate tablet (5 mg) may help to solve this problem. The pros and cons of a small evening dose of a short-acting methylphenidate tablet versus disturbances in falling asleep should be considered.

If additional dosing is necessary, it could be considered that adequate symptom control might be achieved with a twice daily immediate-release methylphenidate regimen.

Treatment should not continue with Ritalin XL capsules if an additional late dose of a short-acting methylphenidate 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.

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 have not been established.

Adults

Ritalin XL is for oral administration once daily usually in the morning. The time of intake may be adapted according to the patient's individual needs.

The maximum daily dose of methylphenidate in adults is 80 mg.

Adult patients new to methylphenidate (see section 5.1):

The recommended starting dose of Ritalin XL in patients who are not currently taking methylphenidate is 20 mg once daily. Treatment with Ritalin XL can also be started with an initial dose of 10 mg daily as per the clinician's judgement (e.g., in patients weighing less than 70 kg). The dose may be adjusted gradually at weekly intervals by a maximum of 20 mg per day. Ritalin XL 10 mg is available for smaller dosage increments.

Adult 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 XL should be made (see below subsection "Switching patient's treatment to Ritalin XL").

Special populations

Elderly (older than 60 years)

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

Hepatic impairment

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

Renal impairment

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

Forgotten doses

The patient should not take a double dose to make up for a forgotten dose. If a dose is forgotten, the patient should wait until it is time for the next dose.

Switching a patient's treatment to Ritalin XL

Ritalin XL administered as a single dose and provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of immediate-release Ritalin administered twice daily (e.g., in the morning and at lunchtime).

The recommended dose of Ritalin XL should be equal to the total daily dose of the immediate-release formulation not exceeding a total dose of 60 mg in children/adolescents and 80 mg in adults.

Examples for the change from tablets (= immediate-release form) to capsules (= modified-release form) can be found in table 1 below:

Table 1

Previous immediate-release methylphenidate dose (Ritalin tablets)	**Recommended Ritalin XL dose**
5 mg twice daily	10 mg once daily
10 mg twice daily	20 mg once daily
15 mg twice daily	30 mg once daily
20 mg twice daily	40 mg once daily
30 mg twice daily	60 mg once daily

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

Long-term (more than 12 months) use

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled clinical trials. Methylphenidate treatment should not and need not be indefinite. When used in children and adolescents with ADHD, treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (more than 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 and adolescents, preferably during school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment should 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.

Method of administration

Ritalin XL capsules are for oral use.

They may be swallowed whole with a drink of water or, alternatively, the capsules may be opened and the contents swallowed after sprinkling onto a small amount of food (see instructions below).

Ritalin XL capsules and/or their contents must not be crushed, chewed, or divided.

Administration by sprinkling capsule contents onto food

The capsules may be carefully opened and the beads sprinkled over soft food (e.g., apple sauce, jam, spread, yoghurt). The food should not be warm because this could affect the modified-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. The distributed beads (e.g., on the apple sauce) must not be chewed or crushed.

Food, drink and alcohol intake

Ritalin XL capsules may be administered with or without food. Taking methylphenidate with food may help to stop abdominal pain, nausea, or vomiting. In case of anorexic effects, methylphenidate should not be taken before a planned meal, but rather with or after the meal.

Patients should abstain from alcohol during treatment (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Glaucoma
- Phaechromocytoma
- During treatment with 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 1) 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, such as cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

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

Long-term use (more than 12 months)

Patients on long-term therapy (i.e., more than 12 months) must have careful ongoing monitoring according to the guidance in section 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 (see also section 4.2).

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 (see section 4.2).

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 adult 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 advised 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 is contraindicated. See section 5.1 under subheading "Clinical studies in adults".

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on 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).**

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 structural cardiac 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 (see section 4.3).

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 disorders

See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is 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. A personal and family history of psychiatric disorders should be systematically sought before starting treatment with methylphenidate (see section 4.2). 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 therapeutic doses (see section 4.8). 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 (see section 4.8). 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 at every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behavioural changes and consider appropriateness of upwards or downwards titration. Treatment interruption may also be considered.

Suicidality

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 discontinuation of methylphenidate should be considered.

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 at every visit.**

Anxiety, agitation or tension

Methylphenidate is associated with the worsening of pre-existing anxiety, agitation, or tension (see section 4.8). 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 months or at every visit.**

Bipolar disorders

Particular care should be taken in using methylphenidate to treat ADHD in patients with co-morbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder; see section 4.3) due to possible acceleration of a mixed/manic episode in these patients. Prior to initiating treatment with methylphenidate, patients with co-morbid 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.**

Priapism

Prolonged and painful erections have been reported in association with methylphenidate, mainly in association with a change in the methylphenidate treatment regimen (see section 4.8). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Growth and weight

Moderately reduced weight gain and growth retardation have been reported with long-term use of methylphenidate in children (see section 4.8).

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

Growth should be monitored in children and adolescents during methylphenidate treatment: height, weight and appetite should be recorded according to the age of the child or adolescent 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 discontinue treatment.

Weight loss has been reported with Ritalin XL treatment in adults. Patients who experience noticeable weight loss during treatment may need to discontinue their treatment. 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 patients 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 (see section 4.8). If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Increased intraocular pressure and glaucoma

There have been reports of increased intraocular pressure (IOP) and glaucoma (including open angle glaucoma and angle closure glaucoma) associated with methylphenidate treatment (see section 4.8). Patients should be advised to contact their doctor in case of experiencing symptoms suggestive of increased IOP and glaucoma. An ophthalmologist should be consulted and discontinuation of methylphenidate be considered if IOP increases (see section 4.3). Ophthalmologic monitoring of patients with a history of increased IOP is recommended.

Haematological effects

In the event of leucopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered. (see section 4.8).

Fatigue

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

Renal or hepatic insufficiency

There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency (see sections 4.2 and 5.2).

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. Acute 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 be taken into account when deciding on a course of treatment for ADHD. Caution is advised in emotionally unstable patients, for example, those

with a history of drug or alcohol dependence, as these patients may increase the dosage on their own.

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

Withdrawal of treatment

Careful supervision is required during 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.

Choice of methylphenidate formulation

The choice of formulation of the methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening

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

Excipients with known effects

This medicine contains sucrose (sugar spheres). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended if combining methylphenidate with other medicinal products, 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. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors).

When starting and stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and to measure their plasma concentrations (or coagulation time for coumarin).

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 other drugs that can also elevate blood pressure (see also section 4.4).

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 14 days) with MAO inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. Patients should therefore abstain from alcohol during treatment.

In case of very high alcohol concentrations, the kinetic profile can change to a profile similar to the immediate-release profile.

Use with anaesthetics

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

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

The long-term safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic drugs

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including levodopa 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 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.

Breast-feeding

Methylphenidate has been found in breast-milk of women 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Ritalin XL may have a moderate influence on the ability to drive and use machines.

Methylphenidate improves attention. However, it may cause dizziness, drowsiness, and visual disturbances including difficulties with accommodation, diplopia, blurred vision, hallucinations, and other side effects on the central nervous system (see section 4.8).

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

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 available data).

Infections and infestations

Common: nasopharyngitis

Uncommon: gastroenteritis[3]

Blood and lymphatic system disorders[1]

Very rare: anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura

Not known: pancytopenia

Immune system disorders

Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rashes, and eruptions

Metabolism and nutrition disorders[1]

Very common: decreased appetite[2]

Common: anorexia, moderately reduced weight and height gain during prolonged use in children[1], weight loss in adults[1]

Psychiatric disorders[1]

Very common: insomnia, nervousness

Common: anorexia, affect lability, aggression[1], agitation[1], anxiety[1], depression[1], irritability, abnormal behaviour, restlessness[2], sleep disorder[2], libido decreased[3], panic attack[3], stress[3], bruxism[3]

Uncommon: psychotic disorders[1], auditory, visual, and tactile hallucinations[1], anger, suicidal ideation[1], mood altered, mood swings, tearfulness, tics[1], worsening of pre-existing tics or Tourette's syndrome[1], hypervigilance, tension[3]

Rare: mania[1], disorientation, libido disorder, obsessive-compulsive disorder (including trichotillomania and dermatillomania)

Very rare: suicidal attempt (including completed suicide)[1], transient depressed mood[1], abnormal thinking, apathy

Not known: delusions[1], thought disturbances[1], confusional state, dependence, logorrhoea.

Cases of abuse and dependence have been described, more often with immediate release formulations

Nervous system disorders

Very common: headache

Common: tremor[2], dizziness, dyskinesia, psychomotor hyperactivity, somnolence

Uncommon: sedation, akathisia[3]

Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS; Reports were poorly documented and, in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).

Not known: cerebrovascular disorders[1] (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions[1], migraine, dysphemia

Eye disorders

Uncommon: diplopia, blurred vision, dry eye[4]

Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Not known: Increased intraocular pressure, glaucoma

Cardiac disorders[1]

Common: arrhythmia, tachycardia, palpitations

Uncommon: chest pain, cardiac murmur[1]

Rare: angina pectoris

Very rare: cardiac arrest, myocardial infarction, sudden cardiac death[1]

Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders[1]

Common: hypertension, peripheral coldness[2]

Very rare: cerebral arteritis and/or occlusion, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Common: cough, pharyngolaryngeal pain, dyspnoea[2]

Not known: epistaxis

Gastrointestinal disorders

Very common: nausea[2], dry mouth[2]

Common: abdominal pain, diarrhoea, stomach discomfort and vomiting, dyspepsia[3], toothache[3]

Uncommon: constipation

Hepatobiliary disorders

Uncommon: hepatic enzyme elevations

Very rare: abnormal liver functions, including hepatic coma

Skin and subcutaneous tissue disorders

Common: hyperhidrosis[2], alopecia, pruritus, rash, urticaria

Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions

Rare: macular rash, erythema

Very rare: erythema multiforme, exfoliate dermatitis, fixed drug eruption

Musculoskeletal and connective tissue disorders

Common: arthralgia

Uncommon: myalgia, muscle twitching, muscle tension[3]

Very rare: muscle cramps

Not known: trismus[3]

Renal and urinary disorders

Uncommon: haematuria

Not known: incontinence

Reproductive system and breast disorders

Rare: gynaecomastia

Not known: erectile dysfunction, priapism[1], increased and prolonged erection[1]

General disorders and administration site conditions

Common: pyrexia, growth retardation during prolonged use in children[1], feeling jittery[3], fatigue[2], thirst[3]

Not known: chest discomfort, hyperpyrexia

Investigations

Common: changes in blood pressure and heart rate (usually an increase) [1], weight decreased[1]

Uncommon: hepatic enzyme increased

Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

[1] See section 4.4 "Special warnings and precautions for use"
[2] ADRs from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents
[3] Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies)
[4] Frequency derived from adult clinical trials and not on data from trials in children and adolescents; may also be relevant for 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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

When treating patients with overdose, the delayed release component of the methylphenidate formulation should be considered.

Signs and symptoms

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

Treatment

There is no specific antidote for methylphenidate overdose. Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate over-stimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be eliminated 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 laxative. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiration; external cooling procedures may be required to reduce 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: psychoanaleptics; psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics

ATC code: N06BA04

Ritalin XL contains a racemate consisting of a 1:1 mixture of d-methylphenidate (d-MPH) and l-methylphenidate (l-MPH). The d-isomer is pharmacologically more active than the l-isomer.

Mechanism of action

Methylphenidate is a CNS stimulant with more prominent effects on central than on motor activities. Its mode of action in humans is not completely understood but its effects are thought to be due to an inhibition of dopamine and norepinephrine reuptake into presynaptic neurons and thereby increasing these neurotransmitters in the extraneuronal space. It is an indirect sympathomimetic.

The central stimulating effect manifests itself in an increase in the ability to concentrate, performance and decision-making, psychophysical activity, and the suppression of tiredness and physical fatigue.

Clinical studies in children and adolescents

Ritalin XL was evaluated in a randomised, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) received a single morning dose of Ritalin LA in the range of 10-40 mg/day, or placebo, for up to 2 weeks. The optimal dose for each patient was determined in a dose titration phase of the study prior to randomization. The primary efficacy variable was the change from baseline to the final rating in the ADHD/DSM-IV Scale for Teachers (CADS-T) total subscale score. CADS-T assesses symptoms of hyperactivity and inattention. The analysis of the primary efficacy variable showed a significant treatment difference in favour of Ritalin LA ($p<0.0001$). A statistically significant treatment effect for Ritalin LA relative to placebo was also found in all analyses of the secondary CADS efficacy variables, as well as in two post-hoc analyses for the ADHD diagnostic subtypes (combined type, inattentive type). The results of the primary and secondary efficacy analyses are summarised in Table 1.

Table 1: ADHD-DSM-IV subscales used by parents (CADS-P) and teachers (CADS-T): variation from baseline value

	Ritalin XL		Placebo		
	n	Mean change[1] (SD[2])	n	Mean change[1] (SD[2])	p-value
CADS-T subscale					
Total	62[3]	10.7 (15.7)	70[3]	-2.8 (10.6)	< 0.0001
Inattentive	62	5.3 (8.25)	70	-1.5 (5.67)	< 0.0001
Hyperactive-Impulsive	62	5.4 (7.95)	70	-1.3 (5.93)	< 0.0001
CADS-P subscale					
Total	63	6.3 (13.5)	70	0.5 (13.55)	0.0043
Inattentive	63	2.8 (7.28)	70	0.2 (6.4)	0.0213
Hyperactive-Impulsive	63	3.5 (6.87)	70	0.3 (7.66)	0.0015

[1]score at end of placebo-washout period minus final score/ [2]standard deviation/ [3]two patients (one in each treatment group) had no CADS-T baseline values but had post-randomization values. They are, therefore, not included in the descriptive statistics.

Clinical studies in adults

Ritalin XL 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 XL without placebo control; Period 3= randomised withdrawal phase). This core study was followed by a 26-week open label extension study.

The core study was a randomised, double-blind, placebo-controlled, multicentre study in the treatment of 725 adult patients (395 males and 330 females) diagnosed with ADHD according to DSM-IV ADHD criteria.

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 period 1. All dose levels of Ritalin XL 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 XL 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).

Clinical efficacy was demonstrated in all three Ritalin XL 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 favour of Ritalin XL over placebo for all assessments in period 1.

Table 2: Analysis of improvement from baseline to end of Period 1 in DSM IV ADHD RS total score and SDS total score by treatment / (LOCF*) for Period 1

		Ritalin XL 40 mg	Ritalin XL 60 mg	Ritalin XL 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 XL was evaluated by measuring the percentage of treatment failure in Ritalin XL compared to the placebo group at the end of a 6-month maintenance period (see Table 3). Once the Ritalin XL 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 XL.

Table 3: Percentage of treatment failures during Period 3

	All Ritalin XL N=352 n (%)	Placebo N=115 n (%)	All Ritalin XL vs placebo 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)
No treatment failure	277 (78.7)	58 (50.4)		

* Two-sided p-value based on comparison between each Ritalin XL 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 XL 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 XL 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 XL 80

mg, whereas for women best improvement was reached in the lowest dose group Ritalin XL 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 (the maximum dose is 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 XL in 298 adult patients with ADHD showed long term safety of Ritalin XL. Combining the continuous exposure to Ritalin XL of all patients treated in the core and the extension studies, a total of 354 patients continuously received Ritalin XL for > 6 months and 136 patients for > 12 months.

No serious unexpected adverse events were observed in this extension study. The safety profile of Ritalin XL did not change with the longer treatment duration of adult ADHD patients. The AE profile seen in the extension patients was similar to that observed in the core study. However, the

total frequency of AEs and the frequency of some specific AEs increased with duration of exposure (<2 months compared with >12 months).

This increased frequency with long-term treatment was shown for decreased weight, insomnia/initial insomnia/sleep disorder, depressed mood (whereas depression decreased over time (0% in > 12 months), high blood pressure, tachycardia and palpitations.

Tachycardia: At baseline, the percentage of patients with a heart rate > 100 bpm was very small (0.4% in the All-Ritalin XL group and 0.6% in the placebo group). Whereas with Ritalin XL 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 XL 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 XL (modified-release capsules) to children/adolescents 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).

50 % of the active substance is contained in immediate-release beads, which produce an initial maximum concentration after approximately 1-2 hours. The remaining 50 % of methylphenidate is contained in delayed-release beads, which dissolve after approximately 4 hours and generate a second peak in plasma concentration 5 to 7 hours after administration.

The time curve of the plasma concentration of Ritalin XL given once daily is comparable to the same total dose of immediate-release methylphenidate (e.g., of Ritalin 10 mg tablets) given twice a day (4 hours apart).

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for Ritalin XL given once a day compared to Ritalin tablets given twice a day.

Food Effects

There was no significant difference in pharmacokinetics of Ritalin XL when administered with either a high fat breakfast or applesauce, compared to administration in the fasting condition. However, food slows absorption and C_{max} levels are reached approximately 1 hour later compared to when individuals were fasting. 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 section 4.2).

Distribution

In the blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Binding of methylphenidate and its metabolites to plasma proteins is low (10-33%). The volume of distribution was 2.23 L/kg (2.65±1.11 L/kg for d-MPH and 1.80±0.91 L/kg for l-MPH) after a single intravenous dose in healthy adult volunteers. Methylphenidate easily crosses the blood-brain barrier.

Biotransformation

Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Peak plasma concentrations of the main, deesterified, metabolite - α-phenyl-2-piperidine acetic acid (ritalinic acid) - are attained approximately 2 hours after administration of methylphenidate and are 30-50 times higher than those of the unchanged substance (methylphenidate). The elimination half-life of ritalinic acid is roughly twice as long as that of methylphenidate, and the mean systemic clearance is 0.17 L/h/kg. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound (methylphenidate). Ritalinic acid has no relevant pharmacological activity.

Elimination

In adults, the plasma elimination half-life of methylphenidate after administration of Ritalin XL is approximately 3.3 hours. The systemic clearance after a single intravenous dose of methylphenidate is 0.565 L/h/kg (0.40±0.12 L/h/kg for d-MPH and 0.73±0.28 L/h/kg for l-MPH) in healthy adult volunteers.

After oral administration, 78 to 97% of the dose is excreted in the urine and 1 to 3% in the faeces in the form of metabolites within 48 to 96 hours. Only small quantities (< 1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60 to 86%), probably pH-independent.

Characteristics in specific groups of patients

Effect of age: There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children (6-13 years) and healthy adult volunteers.

Patients with renal impairment: Elimination data from patients with normal renal function suggest that renal excretion of the unchanged methylphenidate would hardly be diminished at all in the presence of impaired renal function. However, renal excretion of ritalinic acid may be reduced. Since ritalinic acid has little or no pharmacodynamic activity, this appears not to be of concern.

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.

Reproductive and developmental toxicity

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Ammonio methacrylate copolymer type B
Methacrylic acid-methyl methacrylate copolymer (1:1)
Macrogol 6000
Sugar spheres (sucrose and maize starch),
Talc
Triethyl citrate

Capsule shell:
Gelatin
Titanium dioxide (E171)
Printing ink, tan

Printing ink, tan:
Shellac (E904)
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the bottle tightly closed to activate the child-resistant feature of the container closure system.

6.5 Nature and contents of container

High Density Polyethylene (HDPE) bottle with child resistant polypropylene (PP) closure with aluminium induction seal.

Packs of 30 capsules

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

INFECTOPHARM Arzneimittel und Consilium GmbH
Von-Humboldt-Straße 1
64646 Heppenheim
Germany

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