Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medikinet MR 30mg modified – release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-releasecapsule, hard contains 30 mg methylphenidate hydrochloride, equivalent to 25.95 mg methylphenidate.
Excipient with known effect: 69.60 mg – 79.61 mg sucrose/modified-release capsule, hard

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Light grey opaque capsule body/dark violet opaque capsule cap (15.9 mm) containing white and blue pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)
Medikinet MR is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over and 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 an adult psychiatrist.

Special Diagnostic Considerations for ADHD in children

Diagnosis should be made according to current DSM criteria or the guidelines in ICD-10 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 symptoms.

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 medicinal product 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

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 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 pre-existence of childhood ADHD is required and has to be determined retrospectively (by patients' records or if not available by appropriate and structured instruments/interviews). Third-party corroboration is desirable and Medikinet MR should not be initiated when the verification of childhood ADHD symptoms is uncertain. 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

Posology
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 an adult psychiatrist.

Pre-treatment screening:
If required by national practice, in adults new to Medikinet MR, a cardiologist advice is needed prior to treatment initiation in order to check the absence of cardiovascular contraindications. 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 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 in children should be recorded at least 6 monthly with maintenance of a growth chart;
- Weight should be recorded for 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

General aspects:
- 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.
- Children should not take Medikinet MR too late in the morning as it may cause disturbances in sleep.
- For doses not realisable/practicable with this strength, other strengths of this medicinal product and other methylphenidate containing products are available.

Children
Careful dose titration is necessary at the start of treatment with methylphenidate.Dose titration should be started at the lowest possible dose. This is normally achieved using an immediate-release formulation taken in divided doses.The recommended starting daily dose is 5 mg once daily or twice daily (e.g. at breakfast and lunch), increasing if necessary by weekly increments of 5-10 mg in the daily dose according to tolerability and degree of efficacy observed**.** Medikinet MR 10 mg once daily may be used in place of immediate-release methylphenidate hydrochloride 5 mg twice daily from the beginning of treatment where the treating physician considers that twice daily dosing is appropriate from the outset and twice daily treatment administration is impracticable.

Medikinet MR consists of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose). Hence Medikinet MR 10 mg yields an immediate-release dose of 5 mg and an extended-release dose of 5 mg methylphenidate hydrochloride. The extended-release portion of each dose is designed to maintain a treatment response through the afternoon without the need for a midday dose. It is designed to deliver therapeutic plasma levels for a period of approximately 8 hours, which is consistent with the school day rather than the whole day (see section 5.2). For example, 20 mg of Medikinet MR is intended to take the place of 10 mg at breakfast and 10 mg at lunchtime of immediate-release methylphenidate hydrochloride.

Patients currently established on an immediate-release methylphenidate hydrochloride formulation may be switched to the milligram equivalent daily dose of Medikinet MR.
If the effect of the medicinal product wears off too early in the evening, disturbed behaviour may recur.
A small dose (5 mg) of an immediate-release methylphenidate hydrochloride tablet late in the day may help to solve this problem. In that case, it could be considered that adequate symptom control might be achieved with a twice daily immediate-release methylphenidate regimen.
The pros and cons of a small evening dose of immediate-release methylphenidate versus disturbances in falling asleep should be considered.
Treatment should not continue with Medikinet MR if an additional late dose of immediate-release methylphenidate 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.
The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.
The maximum daily dose of methylphenidate hydrochloride in children is 60 mg.

Adults
Continuation of methylphenidate therapy
Adult patients who have shown clear benefit from treatment with Medikinet MR in childhood and/or adolescence may continue treatment with Medikinet MR into adulthood, initially at the same daily dose (mg/day). Whether or not a dose adjustment depending on efficacy and tolerability is necessary or possible must be reviewed regularly.
Adults new to Medikinet MR
Any treatment with methylphenidate requires individual dose titration against efficacy and tolerability because individual response may vary substantially. Initiation of treatment in adults who are new to Medikinet MR therefore requires careful dose titration. Dose titration should be started at the lowest possible dose.
The recommended starting dose is 10 mg daily, which may be increased if necessary by weekly increments of 10 mg in the daily dose according to tolerability and degree of efficacy observed. The total daily dose should be given in two divided doses in the morning and at midday.
The aim of individual titration should be to find the lowest daily dose that achieves satisfactory symptom control.
Compared to children and adolescents, adult patients may require a higher daily dose, based on the patient's body weight.
The maximum daily dose is based on the patient's body weight and must not exceed 1 mg/kg body weight. Regardless of body weight, a maximum daily dose of 80 mg methylphenidate hydrochloride should not be exceeded because limited experience with daily doses greater than 80 mg is available from clinical studies.

Long-term use (more than 12 months)
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment can usually be discontinued during or after puberty, when used in children with ADHD. The physician who elects to use methylphenidate for extended periods (over 12 months) should periodically re-evaluate the long term usefulness of the medicinal product 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 preferably during times of school holidays). Improvement may be sustained when the medicinal product 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.

Elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in patients older than 60 years of age.

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

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

Method of administration
Oral use.
Medikinet MR has to be taken with or after a meal in order to obtain sufficiently prolonged action and to avoid high plasma peaks. Methylphenidate hydrochloride is absorbed much faster from Medikinet MR when the medicinal product is taken on an empty stomach. In this case, release may not be adequately sustained. Therefore, Medikinet MR should not be administered without food.

Children
Medikinet MR should be given in the morning **with** or **after breakfast**.

Adults
Medikinet MR should be given in the morning and at lunchtime **with** or **after the meals**.

The capsules may be swallowed whole with the aid of liquids, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately, and not stored for future use. Drinking some fluids, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Glaucoma
- Phaeochromocytoma
- during treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicinal products, 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
- a history of pronounced anacidity of the stomach with a pH value above 5.5, in therapy with H_2 receptor blockers, proton pump inhibitors or in antacid therapy

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all patients with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the patient's symptoms. When treatment of children is considered, assessment of the severity and chronicity of the child's symptoms should be related to the child's age (6 - 18 years).

Long-term use (more than 12 months)
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. 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 (children), weight, 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) should periodically re-evaluate the long term usefulness of the medicinal product 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 preferably during times of school holidays). Improvement may be sustained when the medicinal product 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 patients older than 60 years of age.

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, exceptional 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.

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 is contraindicated.

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. Methylphenidate should be discontinued in patients under treatment with repeated measures of tachycardia, arrhythmia or increased systolic blood pressure (>95th percentile) and referral to a cardiologist should be considered.

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 patients, 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.

Adults

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

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 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.

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.

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with methylphenidate, the patient should be assessed with regard to pre-existing psychiatric disorders and a family history thereof should be established (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 usual 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. 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 see section 4.8). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome 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

Anxiety, agitation and tension have been reported in patients treated with methylphenidate (see section 4.8). 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 and weight

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 methylphenidate treatment in adults (see section 4.8).
The effects of methylphenidate on final height and final weight are currently unknown and being studied.
Growth should be monitored during methylphenidate treatment. Height, weight and appetite in children 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.

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. In adults, only Medikinet MR should be used.
Caution is advised if long-acting formulations of methylphenidate are used interchangeably due to the differences between these formulations in frequency of dosing, administration with food and plasma drug concentration achieved.

Drug screening

This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.
Athletes must be aware that this medicinal product may cause a positive reaction to 'anti-doping' tests.

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 (see section 4.8).

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.

Excipient: sucrose

This medicinal product contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take this medicine.

Excipient: sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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 medicinal products. Therefore, caution is recommended at 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 (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these medicinal products already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive medicinal products

Methylphenidate may decrease the effectiveness of active substances used to treat hypertension.

Use with medicinal products that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other active substance that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).
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).

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

Use with halogenated anaesthetics
There is a risk of sudden blood pressure and heart rate 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 dopaminergic active substances
Caution is recommended when administering methylphenidate with dopaminergic active substances, 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 DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

Use with other medicines
Medikinet MR must not be taken together with H_2 receptor blockers, proton pump inhibitors or antacids, as this could lead to a faster release of the total amount of active substance.

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 cardio-respiratory toxicity, specifically fetal 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.

Breast-feeding
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 improves attention. However, methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia, blurred vision, hallucinations, and other CNS side effects (see section 4.8). Medikinet MR 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 Medikinet MR and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with Medikinet MR and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used. The table is based on data for children, adolescents and adults.
Frequency estimate:
very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1 000 to <1/100)
rare (≥ 1/10 000 to <1/1 000)
very rare (<1/10 000)
not known (cannot be estimated from the available data)

System Organ Class	Frequency					
	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis	Gastroenteritis			
Blood and lymphatic system disorders					Leucopenia[#], Thrombocytopenia, Anaemia, Thrombocytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as Angioneurotic oedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticaria, Pruritus[*], Rashes, and Eruptions[*]			
Metabolism and nutrition disorders*	Decreased appetite[**]	Anorexia, moderate reduction in weight and height gain during prolonged use in children[*]				
Psychiatric disorders*	Insomnia, Nervousness	Abnormal behaviour, Aggression[*], Affect lability, Agitation**,**	Hypervigilance, Auditory, visual and tactile hallucinations*****,	Mania[*], Disorientation, Libido disorder, Obsessive-comp	Suicidal attempt (including completed suicide)[*], Transient	Delusions[*], Thought disturbances[*],

		Anorexia, Anxiety*, Depression*, Irritability, Restlessness**, Sleep disorder**, Libido decrease***, Panic attack***, Stress***, Bruxism***	Mood altered, Mood swings, Anger, Suicidal ideation*, Tearfulness, Psychotic disorders*, Tics* or Worsening of pre-existing tics of Tourette's syndrome*, Tension***	ulsive disorder (including trichotillomania and dermatillomania)	depressed mood*, Abnormal thinking, Apathy	Confusional state, Dependence, Logorrhoea. Cases of abuse and dependence have been described, more often with immediate-release formulations.
Nervous system disorders	Headache	Tremor**, Somnolence, Dizziness, Dyskinesia, Psychomotor hyperactivity	Sedation, Akathisia***		Convulsions, Choreo-athetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most of cases, patients were also receiving other active substances, so the role of methylphenidate is unclear.)	Cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsions*, Migraine, Paraesthesia$, Aphasia$, Dysphemia
Eye disorders			Diplopia, Blurred vision, Dry eye$	Difficulties in visual accommodation, Mydriasis, Visual disturbance		Ocular hypertension, Increased intraocular pressure, Glaucoma
Ear and labyrinth disorders						Tinnitus$
Cardiac disorders*		Tachycardia**, Palpitations, Arrhythmias	Chest pain	Angina pectoris	Cardiac arrest, Myocardial infarction	Supraventricular tachycardia, Bradycardia, Ventricular extrasystoles, Extrasystol

						es, Cardiac discomfort [$]
Vascular disorders*		Hypertension, Peripheral coldness[**]			Cerebral arteritis and/or occlusion, Raynaud's phenomenon	Hot flush[$], Flushing[$]
Respiratory, thoracic and mediastinal disorders		Cough, Pharyngolaryngeal pain, Dyspnoea[**]				Oropharyngeal pain[$], Epistaxis[$]
Gastrointestinal disorders	Nausea[**], Dry mouth[**]	Abdominal pain, Diarrhoea, Stomach discomfort, Vomiting: - These usually occur at the beginning of treatment and may be alleviated by concomitant food intake. Dyspepsia[***], Toothache[***]	Constipation			Retching[$]
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function, including hepatic coma	
Skin and subcutaneous tissue disorders		Hyperhidrosis[**], Alopecia, Pruritus, Rash, Urticaria	Angioneurotic Oedema, bullous conditions, Exfoliative conditions	Macular rash, Erythema	Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption	
Musculoskeletal and connective tissue disorders		Arthralgia	Myalgia, Muscle twitching, Muscle tightness[***]		Muscle cramps	Trismus[*]
Renal and urinary disorders			Haematuria			Incontinence
Reproductive system and breast disorders				Gynaecomastia		Erectile dysfunction, Priapism, Erection increased and prolonged erection, Breast pain [$]
General disorders and administration site conditions		Pyrexia, Growth retardation during prolonged use in children[*], Feeling of inner restlessness[***], Fatigue[**], Thirst[***]			Sudden cardiac death[*]	Hyperpyrexia, Disturbance in attention[$], Influenza like illness[$],

						Asthenia[$], Chest discomfort
Investigations		Changes in blood pressure and heart rate (usually an increase)[*], Weight decreased[*]	Cardiac murmur[*], Hepatic enzyme increased		Blood alkaline phosphatase increased, Blood bilirubin increased, Platelet count decreased, White blood count abnormal	Blood thyroid stimulating hormone increased[$]
Social circumstances						Partner stress[$], Family stress**

[*]see section 4.4
[**]ADRs from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents
[***]Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies)
[$] 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 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 Medikinet MR

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, dryness of mucous membranes and rhabdomyolysis.

Treatment

There is no specific antidote to Medikinet MR overdose.
Treatmentconsists 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 may 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 hydrochloride has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics

ATC Code: N06BA04

Mechanism of action

Medikinet MRis 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 effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system.

The mechanism by which Medikinet MRexerts its mental and behavioural effects in patients is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system. It is thought to block the re-uptake of norepinephrine and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space. Medikinet MR is a racemic mixture of the d- and l-threo enantiomers of methylphenidate. The d-enantiomer is more pharmacologically active than the l-enantiomer.

Clinical efficacy and safety:

After approval for the treatment of ADHD in children Medikinet MR has been investigated in two randomised, double-blind, placebo-controlled clinical studies on adult patients. 363 patients were investigated in the EMMA study (1) during a treatment period lasting 24 weeks. In the QUMEA study (2) 162 patients were treated for a total of 20 weeks. After the 8-week-double-blind-phase of this, all patients were treated in the open phase for further 12 weeks with Medikinet MR. The main target parameter in both studies was WRI score reduction (Wender-Reimherr-Interview = WRAADS). The measurement time point was week 24 (study 1) or week 8 (study 2).

The daily dose was individually titrated in weekly stages starting with 10 mg a day depending on efficacy and tolerability (study 1) or starting with a dose of 0.5 mg/kg body weight (study 2). A dose of 60 mg a day (study 1) or 1 mg/kg body weight (study 2) should not be exceeded. In the first study, the average dose of methylphenidate at end point was lower, 0.55 mg/kg body weight (administered daily dose min. 10 mg, max. 60 mg) compared with the second study, on average 0.9 mg/kg body weight (administered daily dose min. 20 mg, max. 120 mg). A greater effect size for the whole study population was calculated when administering a higher average dose (0.9 mg/kg body weight), as was the case in the QUMEA study. The clinical studies yielded only limited experience with daily doses of over 80 mg, since only 2 patients were treated with 120 mg/day.

Dose / Gender effects

The results of the first study (EMMA) reveal that gender-specific differences in the response to methylphenidate and the possibility that women could benefit from lower doses cannot be ruled out. This study demonstrated efficacy in men solely in the highest dose range with MPH > 0.7 mg/kg body weight. In women, however, efficacy was demonstrated even in the low (< 0.3 mg/kg body weight) and mid dose range (0.3-0.7 mg/kg body weight). With respect to reduction in symptoms, women in the high dose group showed no significant effect and, with respect to response rate, efficacy was comparable with that in lower dose groups.

In the second study (QUMEA) these gender-specific effects could not be confirmed reliably. This was because the low dose range was not administered and only a few patients were treated in the mid dose range. In the high dose group, the response rate in women was significantly higher in the comparison between verum and placebo. For men, a non-significant result was obtained. With respect to the main target parameter (WRI reduction in week 8), a significant score reduction when compared to placebo was obtained in both men and women.

The following data was obtained for the study population as a whole:

With respect to reduction in the total WRI score in the EMMA study the change from baseline to week 24 was -18.88 on verum compared to -13.99 on placebo, giving an effect size of 0.39, 95% CI (0.18, 0.63, for effect size) p=0.002. (ANOVA using LOCF for missing values). In the QUMEA the change from baseline to week 8 was -13.2 on verum compared to -6.2 on placebo, giving an effect size of 0.54, 95% CI (0.22, 0.85, for effect size) p=0.0001. (ANOVA using LOCF for missing values).

The recalculated responder rate was determined as: Responder: Patients with WRAADDS Score 30% reduction or more and without trial discontinuation, Non-Responder: Patients with less reduction in WRAADDS score or early trial discontinuation for every reason, which lead to missing values in week 24 or 8). In the EMMA trial the recalculated responder rate was 128 (53%) in the verum group vs. 44 (37%) in the placebo group (Week 24, fisher's exact test, two-sided, 0.0051). The recalculated responder rate in the QUMEA study in week 8 was 41 (49%) vs. 14 (18%) (verum versus placebo, fisher's exact test, two-sided, p< 0.0001).

Medikinet MR was also studied in a further randomized, double-blind, placebo-controlled clinical trial (Comparison of Methylphenidate and Psychotherapy Study – COMPAS trial) in 433 adult patients. This study was conducted with Medikinet MR licensed nationally in Germany as "Medikinet adult".

The participants receive either cognitive behavioral group psychotherapy or individual clinical management with the offer for counseling in individual sessions in addition to daily doses of placebo or Medikinet MR. Treatment was conducted for 52 weeks.

The primary outcome of the study was reduction in ADHD symptoms, assessed by a decrease in the CAARS-O: L score from baseline to the end of the first 12-weeks of treatment.

As a result, a combination of group therapy or clinical management with Medikinet MR was superior to the same combination with placebo with respect to an improvement of ADHD symptoms. ADHD symptoms markedly improved during treatment with

Medikinet MR (n = 210; adjusted mean ADHD index score, 16.2; ES = −0.81), as compared to placebo (n = 209; adjusted mean ADHD index score, 17.9; ES = −0.50). The difference was statistically significant (difference in ADHD index score values of Medikinet MR vs. Placebo −1.7; 97.5% CI, −3.0 vs. −0.4; 95% CI, −2.8 vs. −0.6; P = .003).
The average daily dose (SD) in the 179 patients treated with Medikinet MR was 48.8 (20.2) mg.
The COMPAS trial showed that in adults, psychological interventions under controlled conditions rendered a superior treatment outcome (over 52 weeks) when combined with Medikinet MR, as compared to a combination with placebo.

5.2 Pharmacokinetic properties

Absorption
Medikinet MRhas a plasma profile showing two phases of active substance release, with a sharp, initial, upward slope similar to a methylphenidate hydrochloride immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline.
When taken by adults in the morning after breakfast, the immediate-release portion of the hard capsule dissolves rapidly and results in an initial peak plasma concentration. After passing through the stomach and into the small intestine, the sustained-release portion of the hard capsule releases its methylphenidate hydrochloride. This results in the formation of a 3-4 hour plateau phase during which concentrations do not sink below 75% of the peak plasma concentration. The amount of methylphenidate hydrochloride absorbed when administered once daily is comparable with conventional immediate-release formulations administered twice daily.
Medikinet MRcombines the advantages of a fast onset of action with the build-up of an extended-duration plateau phase.
The following pharmacokinetic parameters were measured following a single daily dose of Medikinet MR 20 mg administered after breakfast:
c_{max} = 6.4 ng/ml, t_{max} = 2.75 h, AUC_{inf} = 48.9 ng.h.ml^{-1} and $t_{½}$ = 3.2 h
The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, is proportional to the dose.

Food Effects
Ingestion together with food with a high fat content delays its absorption (t_{max}) by approximately 1.5 hour. There is no difference in bioavailability of Medikinet MR given either a normal or high calorie breakfast. The plasma curves show similar exposure regarding rate and extend of absorption.
It is necessary to take Medikinet MR with or after breakfast. The food influence takes effect and shows a significant and relevant retardation. This justifies the posology to be taken with food. A recommendation in relation of type of food is not necessary. Administration without food can have a risk of dose dumping.

Sprinkle Administration
The c_{max} t_{max} and AUC of the sprinkled contents of the Medikinet MRcapsule are similar (bioequivalent) to the intact capsule. Medikinet MRmay, therefore, be administered either as an intact capsule, or the capsule may be opened and the contents swallowed, without chewing, immediately after sprinkling onto applesauce or other similar soft food.

Availability, systemic
Owing to extensive first-pass metabolism its systemic availability amounts to approximately 30% (11-51%) of the dose.

Distribution
In the blood, methylphenidate and its metabolites become distributed in the plasma (57%) and the erythrocytes (43%). Methylphenidate and its metabolites have a low plasma protein-binding (10-33%). The volume of distribution after a single intravenous dose is 2.2 l/kg (2.65±1.1 l/kg for d-methylphenidate and 1.8±0.9 l/kg for l-methylphenidate).

Elimination
Methylphenidate is eliminated from the plasma with an average half-life of approximately 2 hours. The mean clearance after an intravenous single dose is 0.565 l/h/kg (0.40±0.12 l/h/kg for d-methylphenidate and 0.73±0.28 l/h/kg for l-methylphenidate). After oral administration, approximately 78-97% of the dose is excreted within 48 to 96 h via the urine and 1 to 3% via the faeces in the form of metabolites. Only small amounts (< 1%) of unchanged methylphenidate appear in the urine. A large proportion of an intravenous dose (89%) is eliminated in the urine within 16 hours, presumably regardless of the pH value, as ritalinic acid.
The renal elimination of ritalinic acid may decrease in the case of impaired renal function.
The bulk of the dose is excreted in the urine as 2-phenyl-2-piperidyl acetic acid (PPAA, 60-86%).

Pharmacokinetics in special patient groups

Paediatric population

The pharmacokinetics of Medikinet MR in children younger 6 years of age have not been studied.
There are apparently no differences in the pharmacokinetics of methylphenidate between children with hyperkinetic disorder/ADHD and healthy adult subjects.

Elderly
The pharmacokinetics of Medikinet MR in patients aged 65 years and over have not been studied.

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 PPAA 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Sugar spheres (sucrose, maize starch)
Methacrylic acid-ethylacrylate-copolymer (1:1)
Talc
Triethyl citrate
Poly(vinyl alcohol)
Macrogol 3350
Polysorbate 80
Sodium hydroxide
Sodium laurilsulfate
Simeticone
Silica colloidal anhydrous
Methylcellulose
Sorbic acid
Indigo carmine, aluminium lake (E 132)

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Sodium laurilsulfate
Purified water
Erythrosine (E 127)
Iron oxide black (E172)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Boxes of 28 or 30 modified-release capsules, hard in PVC/PVdC blisters heat sealed to aluminium foil.

Not all pack sizes may be marketed.

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

Medice Arzneimittel Putter GmbH & Co. K.G
Kuhloweg 37
58638 Iserlohn
Germany

8 MARKETING AUTHORISATION NUMBER

PA1555/001/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th May 2011
Date of last renewal: 11th November 2013

10 DATE OF REVISION OF THE TEXT

April 2026