# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Medikinet 20 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg methylphenidate hydrochloride, equivalent to 17.30 mg methylphenidate.
Excipient with known effect: 38.48 mg lactose/tablet
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.
White, round tablet with a break score on both sides and notches at the edges embossed with ”L” on both halves.
The tablet can be divided into equal halves.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Attention-Deficit/Hyperactivity Disorder (ADHD)**
Medikinet is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be initiated under the supervision of a specialist in childhood behaviour disorders.
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.

### 4.2 Posology and method of administration

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

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

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

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

**Dose titration**
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose. The effect occurs within an hour after ingestion if the dose is sufficiently high.

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. Doses above 60 mg daily are not recommended. The total daily dose should be administered in divided doses (usually 2-3).
For doses not realisable/practicable with this strength, other strengths of this medicinal product and other methylphenidate containing products are available.
In the treatment of hyperkinetic disorders/ADHD, the times at which the doses of Medikinet are administered should be selected to provide the best effect when it is most needed to combat school and social behavioural difficulties.

The last doses should, in general, not be given within 4 hours before bedtime in order to prevent disturbances in falling asleep. However, if the effect of the medicinal product wears off too early in the evening, disturbed behaviour may recur. A small evening dose (5 mg) may help to solve this problem.
The pros and cons of a small evening dose versus disturbances in falling asleep should be considered.
The maximum daily dose of methylphenidate hydrochloride is 60 mg.

**Long-term (more than 12 months) use in children and adolescents**
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 is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the 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 child's condition (preferable 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.

**Adults**
Medikinet is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group.

**Elderly**
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

**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.
The tablets should be swallowed whole or divided into halves with the aid of liquids, either with meals or after meals.

The effect of food on the absorption of methylphenidate from Medikinet tablets has not been studied; therefore, a possible effect of food on absorption cannot be excluded. Therefore it is recommended that Medikinet tablets should be taken in a standardised manner in relation to the timing of meals, i.e. that doses should be given at same times, relative to the time of meals, on each day, preferably with or immediately after meals.

**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

**4.4 Special warnings and precautions for use**

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 (6 - 18 years).

**Long-term use (more than 12 months) in children and adolescents**
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 is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth, appetite, development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.
The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the 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 child's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

**Use in adults**
Medikinet is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group.

**Use in the elderly**
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

**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. 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.
The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric 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 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 children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

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

**Cerebrovascular disorders**
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment 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 symptomscould 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 children and adolescents 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 in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

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

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

**Growth**
Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children (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 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.

**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.

**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).

**Excipient: lactose**
This medicinal product contains lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**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. It is therefore advisable for patients to abstain from alcohol during treatment.

**Use with food**

No studies have been performed to study a possible food effect. Therefore it is recommended to take Medikinet tablets in a standardised manner in relation to the timing of meals, i.e. that doses should be given at same times, relative to the time of meals, on each day, preferably with or immediately after meals (see section 4.2).

**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.

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

**Infections and infestations**
Common: nasopharyngitis
Uncommon: gastroenteritis

**Blood and lymphatic system disorders**
Very rare: leukopenia, thrombocytopenia, anaemia, 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***
Very common: decreased appetite**
Common: anorexia, moderate reduction in weight and height gain during prolonged use in children*

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

**Nervous system disorders**
Very common: headache
Common: tremor**, somnolence, dizziness, dyskinesia, psychomotor hyperactivity
Uncommon: sedation, akathisia***
Very rare: 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.)
Not known: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebral arteritis, cerebral occlusion and cerebrovascular accidents), grand mal convulsions*, migraine, dysphemia

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

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

**Vascular disorders***
Common: hypertension, peripheral coldness**

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

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

**Gastrointestinal disorders**
Very common: nausea**, dry mouth**
Common: abdominal pain, stomach discomfort, vomiting, dyspepsia***, toothache***, diarrhoea (these usually occur at the beginning of treatment and may be alleviated by concomitant food intake.)
Uncommon: constipation

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

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

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

**Renal and urinary disorders**
Uncommon: haematuria
Not known: incontinence

**Reproductive system and breast disorders**
Rare: gynaecomastia
Not known: erectile dysfunction, priapism, erection increased and prolonged erection

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

**Investigations**
Common: changes in blood pressure and heart rate (usually an increase)*, weight decreased*
Uncommon: cardiac murmur*, hepatic enzyme increased
Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal
*see section 4.4
**ADRs from clinical trials in adult patients that were reported at 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)

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**

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 overdose.
Treatment consists of appropriate supportive measures.
The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine 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

Pharmacotherapeutic group: psychoanaleptics, psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics
ATC Code: N06BA04
Mechanism of action
Medikinet is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood but its effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system.
The mechanism by which Medikinet exerts its mental and behavioural effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system. 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 is a racemic mixture of the d- and l-threo enantiomers of methylphenidate. The d-enantiomer is more pharmacologically active than the l-enantiomer.

### 5.2 Pharmacokinetic properties

Absorption
Medikinet is rapidly and almost completely absorbed. Owing to its pronounced “first-pass” metabolism the absolute bioavailability is low at only 30 % (11-51 %) of the dose. Absorption is accelerated when the medicinal product is taken with meals but has no effect on the total amount absorbed. Maximum plasma concentrations of 7 ng/ml are reached on average 1-2 hours after administration of 10 mg. The maximum plasma concentrations vary considerably interindividually.
There are considerable interindividual and intraindividual variations in the plasma concentrations which, however, provide little conclusive evidence of the therapeutic efficacy. The relatively short half-life correlates well with the duration of action of 1 to 4 hours.
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).
Biotransformation
Biotransformation of methylphenidate is rapid and extensive. Peak plasma concentrations of 2-phenyl -2-piperidyl acetic acid (PPAA) are attained approximately 2 hours after administration of methylphenidate and are 30 - 50 times higher than those of the unchanged substance. The half-life of PPAA 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.
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.
There is apparently no difference in the pharmacokinetics of methylphenidate between children with hyperkinetic disorders/ ADHD and healthy adult test subjects. Pharmacokinetic properties of methylphenidate have not been studied in children below 6 years of age or in elderly above 65 years.
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%).
Characteristics in patients
There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and healthy adult volunteers.
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**

Microcrystalline cellulose
Pregelatinised maize starch
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Do not store above 25 °C.
Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

Boxes containing 28 or 30tabletspackaged in PVC/PVdC white opaqueblisters heat sealed to aluminium foil.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

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

**8 MARKETING AUTHORISATION NUMBER**

PA1555/001/008

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25th February 2011
Date of last renewal: 11th November 2013

**10 DATE OF REVISION OF THE TEXT**

November 2022