PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

MEDIKINET MR 5 mg capsules

MEDIKINET MR 10 mg capsules

MEDIKINET MR 20 mg capsules

MEDIKINET MR 30 mg capsules

MEDIKINET MR 40 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MEDIKINET MR 5 mg capsules

Each capsule contains 5 mg methylphenidate hydrochloride, corresponding to 4.35 mg methylphenidate.

Excipients: 63.57 mg – 72.71 mg sucrose/capsule

MEDIKINET MR 10 mg capsules

Each capsule contains 10 mg methylphenidate hydrochloride, corresponding to 8.65 mg methylphenidate.

Excipients: 127.14 mg – 145.42 mg sucrose/capsule

MEDIKINET MR 20 mg capsules

Each capsule contains 20 mg methylphenidate hydrochloride, corresponding to 17.30 mg methylphenidate.

Excipients: 114.65 mg – 131.13 mg sucrose/capsule

MEDIKINET MR 30 mg capsules

Each capsule contains 30 mg methylphenidate hydrochloride, corresponding to 25.95 mg methylphenidate.

Excipients: 69.60 mg – 79.61 mg sucrose/capsule

MEDIKINET MR 40 mg capsules

Each modified-release capsule contains 40 mg methylphenidate hydrochloride, corresponding to 34.60 mg methylphenidate.

Excipients: 92.80 mg – 106.14 mg sucrose/capsule

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsules, hard

MEDIKINET MR 5 mg capsules

White opaque capsules size 3 with a black imprint containing white and blue pellets.

MEDIKINET MR 10 mg capsules

Amethyst-white opaque capsules size 3 with a black imprint containing white and blue pellets.

MEDIKINET MR 20 mg capsules

Amethyst opaque capsules size 3 with a black imprint containing white and blue pellets.

MEDIKINET MR 30 mg capsules

Hard capsules size 3 with a dark violet opaque cap with a white imprint and a light grey opaque body with a black imprint containing white and blue pellets.

MEDIKINET MR 40 mg capsules

Hard capsules size 2 with dark violet opaque cap with a white imprint and a grey opaque body with a black imprint 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) when remedial measures alone prove insufficient. Treatment must be initiated under the supervision of a specialist in behavioural disorders.

Diagnosis should be made considering DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. For adults, this includes a structured interview of the patient to determine current symptoms, also comprising scales for self-assessment as well as a retrospective determination of the preexistence of ADHD during childhood, which has to be conducted using validated instruments. Diagnosis cannot be made solely on the presence of one or more symptoms.

The specific aetiology of this syndrome is unknown. There is no single diagnostic test. Adequate diagnosis requires the use of medical, specialised psychological, and (for children and adolescents) educational, as well as social resources.

A comprehensive treatment programme typically includes psychological, social, and (for children and adolescents) educational measures, as well as pharmacotherapy and is aimed at stabilising patients 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 patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the symptoms.

Appropriate psychopathological or (for children and adolescents) 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 symptoms. The use of methylphenidate should always follow the licensed indication and prescribing / diagnostic guidelines.

4.2 Posology and method of administration

Treatment must be initiated under the supervision of a specialist in behavioural disorders.

<u>Pre-treatment screening</u>:

Prior to a prescription, the cardiovascular status of the patient, including blood pressure

and pulse rate, has to be evaluated. A comprehensive anamnesis should comprise concomitant medication, past and present physical and psychiatric comorbidities or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment body weight (see sections 4.3 and 4.4).

For children and adolescents, also body height should be documented using a growth chart.

Ongoing monitoring

Body weight, (for children and adolescents also body height) 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;
- body weight and appetite should be recorded at least 6 monthly with maintenance of a chart;
- development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit;
- in children and adolescents, body height should be recorded at least 6 monthly with maintenance of a growth chart

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

Dose titration

Treatment with methylphenidate requires individual dosing according to the observed degree of efficacy and tolerability, as the individual response may vary broadly. Hence, careful dose titration is necessary at the start of treatment with MEDIKINET MR. Dose titration should be started at a dose as low as possible.

Initiation of treatment with MEDIKINET MR in children and adolescents

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.

Children and adolescents currently using methylphenidate hydrochloride

Patients established on an immediate-release methylphenidate hydrochloride formulation may be switched to the milligram equivalent daily dose of MEDIKINET MR.

MEDIKINET MR should not be taken too late in the morning as it may cause disturbances in sleep.

However, if the effect of the medicinal product wears off too early in the evening, disturbed behaviour may recur.

A small dose 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 maximum daily dose of methylphenidate hydrochloride is 60 mg.

Continuation of treatment into adulthood

In adults who had unambiguously profited from treatment with MEDIKINET MR during childhood or adolescence, treatment with MEDIKINET MR may initially be continued at the same daily dose (mg/day). It has to be regularly checked if an adjustment of the dose is necessary or feasible, depending on efficacy and tolerability. Adult patients may require a higher daily dose, as compared to children and adolescents. The maximum daily dose should be based on the body weight of the patient and must not exceed 1 mg/kg body weight. However, the maximum daily dose should not exceed 80 mg, independent of the body weight of the patient, as only limited experience with total daily doses higher than 80 mg are available from clinical studies.

Initiation of treatment with MEDIKINET MR in adults

The recommended starting daily dose is 10 mg. If necessary, the daily dose may be increased by weekly increments of 10 mg according to tolerability and degree of efficacy observed.

The total daily dose should be divided into two administrations, in the morning and at noon. The target of the individual dose titration should be the lowest total daily dose that achieves satisfactory symptom control. The maximum daily dose should be based on body weight of the patient and must not exceed 1 mg/kg body weight. However, the maximum daily dose should not exceed 80 mg, independent of the body weight of the patient, as only limited experience with total daily doses higher than 80 mg are available from clinical studies.

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 contains an immediate-release dose of 5 mg and an extended release dose of 5 mg methylphenidate hydrochloride.

Thus, MEDIKINET MR is designed to deliver therapeutic plasma levels for a time period of approximately 8 hours.

Therefore, children and adolescents shall take a single dose of MEDIKINET MR in the morning with or after breakfast in order to obtain a sufficiently prolonged throughout the school day.

Adults shall usually divide their total daily dose of MEDIKINET MR into two equal doses and shall take one dose in the morning and one at lunchtime, each with or after a meal in order to obtain a sufficiently prolonged action throughout the day (see section 5.2).

If other formulations of methylphenidate should be substituted, it should be kept in mind that MEDIKINET MR has to be administered with food. Conditions leading to increased gastric pH have to be avoided. In this case, release may not be adequately sustained.

MEDIKINET MR has to be taken with or after the meal in order to obtain sufficiently prolonged action and to avoid high plasma peaks. Methylphenidate 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.

The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

For doses not realisable/practicable with this strength, other strengths of this medicinal product and other methylphenidate containing products are available.

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 or yoghurt. In this case food should be eaten as well, of course. The capsules and the capsule contents must not be crushed or chewed.

Long-term (more than 12 months)

The safety and efficacy of long-term use of MEDIKINET MR for more than 6 months has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and needs not to be indefinite. The physician who elects to use methylphenidate for extended periods (over 12 months) in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the patient's condition (for children and adolescent preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

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

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.

4.3 Contraindications

- known sensitivity to methylphenidate or any of the excipients
- anxiety, tension
- agitation
- glaucoma
- phaeochromocytoma
- during treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis (see section 4.5)
- hyperthyroidism or thyrotoxicosis
- diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- diagnosis or history of severe and episodic (type I) bipolar (affective) disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina pectoris, 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
- diagnosis of pronounced anacidity of the stomach with a pH value above 5.5, in therapy with H_2 receptor blockers or in antacid therapy or proton pump inhibitors
- Diagnosis or family history of Tourette's syndrome

4.4 Special warnings and special precautions for use

General

Treatment with methylphenidate is not indicated in all cases of attention-deficit/hyperactivity disorder, and should be considered only after detailed history-taking and evaluation. The decision to prescribe methylphenidate should depend on an assessment of the severity of symptoms and, in pediatric patients, their appropriateness to the child's age, and not simply on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Cardiovascular

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in patients with structural cardiac abnormalities or other serious problems. A causul relationship with stimulant products has not been established since some of these conditions alone may carry an increased risk of sudden death. Stimulant products, including methylphenidate, generally should not be used in patients with known structural cardiac abnormalities or other serious cardiac disorders that may increase the risk of sudden death due to sympathomimetic effects of a stimulant drug. Before initiating methylphenidate treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see section Dosage and Administration).

Cardiovascular Conditions

Methylphenidate is contraindicated in patients with severe hypertension. Methylphenidate increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension, severe cardiovascular disorders are contraindicated (see section Contraindications).

Blood pressure should be monitored at appropriate intervals in all patients taking methylphenidate, especially in those with hypertension. Patients who develop symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt cardiac evaluation.

Misuse and Cardiovascular Events

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

Cerebrovascular Cerebrovascular Conditions

Patients with pre-existing central nervous system (CNS) abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with methylphenidate. Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with methylphenidate (see above paragraph on Cardiovascular Conditions and section Interactions).

Psychiatric

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with methylphenidate, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section Dosage and Administration). Treatment of ADHD with stimulant products including methylphenidate should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, methylphenidate should not be given to patients unless the benefit outweighs the potential risk.

Psychotic Symptoms

Psychotic symptoms, including visual and tactile hallucinations or mania have been reported in patients administered usual prescribed doses of stimulant products, including methylphenidate (see section Adverse Drug Reactions). Physicians should consider treatment discontinuation.

Depression or Psychosis

Methylphenidate should not be used as treatment for severe depression of either exogenous or endogenous origin. In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

Treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

Aggressive Behavior

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

Suicidal Tendency

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

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 Adverse Drug Reactions). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate for ADHD treatment. Methylphenidate is contraindicated in case of diagnosis or family history of Tourette's syndrome (see section Contraindications). Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.

Growth Retardation

Moderately reduced weight gain and slight growth retardation have been reported with the long-term use of stimulants, including methylphenidate, in children (see section Adverse Drug Reactions). Growth should be monitored as clinically necessary during treatment with methylphenidate, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsion threshold in patients with a history of seizures, with prior EEG abnormalities in the absence of seizures and, rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, the drug should be discontinued.

Methylphenidate should be used with caution in patients with epilepsy as clinical experience has shown that it can cause an increase in seizure frequency in a small number of such patients. If seizure frequency increases, methylphenidate should be discontinued.

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Drug Abuse and Dependence

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially with parenteral abuse. Clinical data indicate that children given methylphenidate are not more likely to abuse drugs as adolescents or adults. Caution is called for in emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because they may increase the dosage on their own initiative.

Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as the effects of chronic overactivity. Some patients may require long-term follow-up.

Hematological Effects

The long-term safety and efficacy profiles of methylphenidate are not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. In the event of haematological disorders appropriate medical intervention should be considered (see section Adverse Drug Reactions).

Pediatric Patients under 6 years of age

Methylphenidate should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

Driving and Using Machines

Methylphenidate may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see section Adverse Drug Reactions). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

Other Drug Dependence

As with other stimulants, the possibility of habituation or abuse must be considered, particularly in emotionally unstable patients and those with a history of drug dependence or alcoholism, because such patients may increase the dose on their own initiative. Alcohol may exacerbate the CNS adverse reactions of psychoactive drugs, including methylphenidate. Therefore, it is advisable for patients to abstain from alcohol during treatment.

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

Careful supervision is required during drug withdrawal, since this may unmask depression as well as the effects of chronic overactivity. Some patients may require long-term follow-up.

Excipients: Sucrose Intolerance

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.

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic interaction

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

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

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

Pharmacodynamic interactions

Anti-hypertensive drugs

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

Use with drugs that elevate blood pressure

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

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 drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics

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

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

Serious, adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic drugs

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.

The coadministration of methylphenidate with antipsychotics is not recommended because of the counteracting mechanism of action.

Use with other drugs

MEDIKINET MR must not be administered together with H_2 receptor blockers or antacids, as this may lead to an accelerated liberation of the total amount of active substance.

Drug/Laboratory Test

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

4.6 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 foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

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

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

Lactation

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5 (see section Clinical Pharmacology, Pharmacokinetics). For safety reasons, mothers taking methylphenidate should refrain from breast-feeding their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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 disorders

Very rare: anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Unknown: pancytopenia

Immune system disorders

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

Metabolism and nutritional disorders*

Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*

Psychiatric disorders*

Very common: insomnia, nervousness

Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour, panic attack**, stress**, bruxism∞

Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder, 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.

Cases of abuse and dependence have been described, more often with immediate-release formulations (frequency not known).

Nervous system disorders

Very common: headache

Common: dizziness, dyskinesia, psychomotor hyperactivity, somnolence Uncommon: sedation, tremor, akathisia**

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

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

Eye disorders

Uncommon: diplopia, blurred vision,

Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*

Common: arrhythmia, tachycardia, palpitations Uncommon: chest pain

Rare: angina pectoris

Very rare: cardiac arrest, myocardial infarction

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

Vascular disorders*

Common: hypertension

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

Respiratory, thoracic, and mediastinal disorders

Common: cough, pharyngolaryngeal pain

Uncommon: dyspnoea

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, nausea, stomach discomfort, and vomiting: - These usually occur at the beginning of treatment and may be alleviated by concomitant food intake, dry mouth, dyspepsia**, toothache**

Uncommon: constipation

Hepatobiliary disorders

Uncommon: hepatic enzyme elevations

Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders

Common: alopecia, pruritus, rash, urticaria, hyperhidrosis$

Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions

Rare: macular rash, erythema

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

Not known: dry skin

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia

Uncommon: myalgia, muscle twitching, muscle tightness**

Very rare: muscle cramps

Not known: trismus∞

Renal and urinary disorders

Uncommon: haematuria

Not known: incontinence

Reproductive system and breast disorders

Rare: Gynaecomastia, menstruation disorder#, impairment of libido#

Not known: Menstruation disturbances

General disorders and administration site conditions

Common: pyrexia, growth retardation during prolonged use in children*

Uncommon: chest pain, fatigue, thirst**

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 not reported in children and adolescents

Frequency derived from clinical trials in adult patients but may be also relevant for children and adolescents.

$ ADR 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)

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 an overdose of MEDIKINET MR. Treatment consists of appropriate supportive measures.

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

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: N06BA04

Mechanism of action:

MEDIKINET MR 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 MR exerts its mental and behavioural effects 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 neurones 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.

MEDIKINET MR was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients: 363 patients were evaluated in the EMMA study (1) using a treatment duration of 24 weeks. In the QUMEA study (2), 162 patients were treated for 20 weeks overall, with all patients having changed from an 8-week double-blinded phase to an open phase of 12 weeks, during which all patients were treated with MEDIKINET MR. Primary endpoint of both studies was a decrease in WRI score (Wender-Reimherr-Interview = WRAADS). Evaluation took place at week 24 (study 1) and week 8 (study 2).

The daily dose was titrated individually in weekly steps according to the observed efficacy and tolerability, starting with 10 mg per day (study 1) or with a dose of 0.5 mg/kg body weight (study 2). It was planned not to exceed a total daily dose of 60 mg (study 1) or 1 mg/kg body weight (study 2). At evaluation of the studies, methylphenidate was dosed lower in the first study, with the average value being 0.55 mg/kg body weight (administered daily dose: min. 10 mg, max. 60 mg), as compared to the second study, with the average value being

0.9 mg/kg body weight (administered daily dose: min. 20 mg, max. 120 mg). A higher effect size for the whole study population was calculated for the administration of a higher average dose (0.9 mg/kg body weight), as it was the case in the QUMEA study. The clinical studies rendered only limited experience with total daily doses of more than 80 mg, since only two patients were treated with daily doses of 120 mg/day.

Dose/gender effect

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).

5.2 Pharmacokinetic properties Absorption:

MEDIKINET MR has 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 MR combines 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 hours. There is no difference in bioavailability of MEDIKINET MR given either with a normal or high calorie meal. The plasma curves show similar exposure regarding rate and extend of absorption.

It is necessary to take MEDIKINET MR with or after a meal. 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 MR capsule are similar (bioequivalent) to the intact capsule. MEDIKINET MR may, 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.

Age:

The pharmacokinetics of MEDIKINET MR have not been studied in children younger than 6 years of age and in adults older than 65 years of age.

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 plasma (57%) and 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.

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

Reproductive Toxicity

Methylphenidate is considered to be possibly teratogenic in rabbits. Spina bifida with malrotated hind limbs was observed in two separate litters at a dose of 200mg/kg/day.

Exposure (AUC) at this dose was approximately 5.1 times higher than the extrapolated exposure at the maximum recommended human dose (MRHD). Exposure at the next lower dose, wherein no spina bifida was found, was 0.7 times the extrapolated exposure at MRHD. A second study was conducted with a high dose of 300 mg/kg, which was considered maternally toxic. No spina bifida was seen, in 12 liters (92 fetuses) surviving. Exposure (AUC) at 300 mg/kg was 7.5 times the extrapolated exposure at MRHD.

Methylphenidate is not teratogenic in rats. Development fetal toxicity was noted at a high dose of 75 mg/kg (20.9 times higher than the exposure (AUC) at MRHD) and consisted of an increase of the instance of fetuses with delayed ossification of the skull and hyoid bones as well as fetuses with short supernumerary ribs.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted over two generations of mice continously receiving methylphenidate doses of up to 160 mg/kg/day (about 90-fold* higher than the MRHD on a mg/kg basis).

*based on pediatric patient body weight of 35 kg and a MRHD of 60 mg/day

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis), offspring body weight gain was decreased at the highest dose, but no other effects on postnatal development were observed.

Carcinogenicity

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas (a benign tumor) and, in males only, an increase in hepatoblastomas (a malignant tumor) at daily doses of approximately 60 mg/kg/day about 35-fold-higher than the MRHD on a mg/kg basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no overall increase in the number of malignant hepatic tumors. The mouse strain used is particularly sensitive to the development of hepatic tumors. It is thought that hepatoblastomas might be due to non-genotoxic mechanisms such as an increase in hepatic cell proliferation. This is consistent with the increase in liver weights observed in this mouse carcinogenicity study.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day (about 26-fold* higher than the MRHD on a mg/kg basis).

*based on pediatric patient body weight of 35 kg and a MRHD of 60 mg/day

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

in the capsule content:

Sugar spheres (sucrose, maize starch), Methacrylic acid-ethylacrylate-copolymer (1:1) dispersion 30%, Talc, Triethyl citrate, Poly(vinyl alcohol), Macrogol 3350, Polysorbate 80, Sodium hydroxide, Sodium laurilsulfate, Simeticone emulsion 30%, Silica colloidal anhydrous, Methylcellulose, Sorbic acid, Indigo carmine, aluminium lake (E 132)

in the capsule shell:

Gelatin, Titanium dioxide (E 171)

additional in the capsule shell of MEDIKINET MR 10 mg and 20 mg:

Erythrosine (E 127), Brilliant Blue FCF (E 133)

additional in the capsule shell of MEDIKINET MR 30 mg and 40 mg:

Erythrosine (E 127), Brilliant Blue FCF (E 133), Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MEDIKINET MR 5 mg and 10 mg:

24 months

MEDIKINET MR 20 mg, 30 mg and 40 mg:

36 months

6.4 Special precautions for storage

Do not store above 30 °C.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of the container

MEDIKINET MR 5 mg:

Box of 30 capsules in PVC/PCTFE/PVC white opaque blisters heat-sealed to aluminium foil.

MEDIKINET MR 10 mg, 20 mg, 30 mg and 40 mg:

Box of 30 capsules in PVC/PCTFE/PVC or PVC/PVDC white opaque blisters heat-sealed to aluminium foil.

6.6 Instructions for use/handling

No special requirements.

7. NAME AND ADDRESS OF THE MANUFACTURER

Medice Arzneimittel Pütter GmbH & Co. KG

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Germany

8. DATE OF REVISION OF TEXT

April 2022