SmPC

(Medice – dated 12.2011)

1. NAME OF THE MEDICINAL PRODUCT

MEDIKINET MR 5 mg modified-release capsules
MEDIKINET MR 10 mg modified-release capsules
MEDIKINET MR 20 mg modified-release capsules
MEDIKINET MR 30 mg modified-release capsules
MEDIKINET MR 40 mg modified-release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MEDIKINET MR 5 mg modified-release capsules
Each modified-release 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 modified-release capsules
Each modified-release 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 modified-release capsules
Each modified-release 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 modified-release capsules
Each modified-release 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 modified-release 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 capsule, hard.

MEDIKINET MR 5 mg modified-release capsules, hard

White opaque hard capsules containing white and blue pellets.

MEDIKINET MR 10 mg modified-release capsules, hard

Hard capsules with mauve opaque cap and white opaque body containing white and blue pellets.

MEDIKINET MR 20 mg modified-release capsules, hard

Mauve opaque hard capsules containing white and blue pellets.

MEDIKINET MR 30 mg modified-release capsules, hard

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

MEDIKINET MR 40 mg modified-release capsules, hard

Hard capsules with dark violet opaque cap and a grey opaque body containing white and blue pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)

Medikinet MR is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over 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 DSM-IV 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.

Additional information on the safe use of the medicinal product:

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.

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

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of Medikinet MR 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

Treatment must be initiated under the supervision of a specialist in childhood behaviour 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 Medikinet MR.

Dose titration:
Careful dose titration is necessary at the start of treatment with methylphenidate. **.** 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.
The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

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

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

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

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 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 maximum daily dosage of methylphenidate is 60 mg.

MEDIKINET MR should be given in the morning with or after breakfast.

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) 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 drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

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

Adults

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

Elderly

Medikinet MR should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age

Medikinet MR 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
- in patients with marked anxiety, agitation or tension as the use of Medikinet MR may aggravate these symptoms
- 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 and hyperthermia (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, history of aggression
- in patients with known drug dependence or alcoholism
- in patients with motor tics, tics in siblings, or a family history or diagnosis of Tourette's syndrome

- 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, cardiac arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke
- a history of pronounced anacidity of the stomach with a pH value above 5.5, in therapy with H_2 receptor blockers or in antacid therapy

4.4 Special warnings and special precautions for use

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

Long-term use (more than 12 months) in children and adolescents

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

Use in adults

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

Use in the elderly

Medikinet MR 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

Medikinet MR 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 Medikinet MR 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 in 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 Medikinet MR 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 Medikinet MR 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 Medikinet MR.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

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

Psychiatric disorders

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

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

Exacerbation of pre-existing psychotic or manic symptoms

In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur,

consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour

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

Clinical experience suggests that Medikinet MR may exacerbate symptoms of behavioural disturbance and thought disorder in psychotic children

Medikinet MR should not be used to treat severe exogenous or endogenous depression.

Suicidal tendency

Medikinet MR should be administered with caution to patients with severe depression or with suicidal thoughts or actions because there is a risk of aggravation of this condition.

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

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in 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

Medikinet MR 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 Medikinet MR 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 Medikinet MR, 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.

The effects of Medikinet MR 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

Medikinet MR should be used with caution in patients with epilepsy. Medikinet MR 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, Medikinet MR should be discontinued.

Abuse, misuse and diversion

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

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

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

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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

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

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

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

Pharmacodynamic interactions

Anti-hypertensive drugs

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

Methylphenidate may also decrease the antihypertensive effect of guanethidine.

Use with drugs that elevate blood pressure

Caution is advised in patients being treated with Medikinet MR 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, Medikinet MR 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

Possible interactions with antipsychotics (haloperidol and thioridazine) have also been reported.

Use with domapinergic drugs

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

Medikinet MR must not be taken together with H2 receptor blockers or antacids, as this could lead to a faster release of the total amount of active substance.

4.6 Pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of methylphenidate in pregnant women.

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.

Lactation

Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Medikinet MR 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 ADRs with MEDIKINET MR and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:

very common (≥ 1/10)

common (≥ 1/100 to < 1/10)

uncommon (≥ 1/1000 to <1/100)

rare (≥ 1/10,000 to <1/1000)

very rare (<1/10,000)

not known (cannot be estimated from the available data).

Infections and infestations

Common: nasopharyngitis

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

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

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

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

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

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

Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions

Rare: hyperhidrosis, 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

Very rare: muscle cramps

Renal and urinary disorders

Uncommon: haematuria

Reproductive system and breast disorders

Rare: gynaecomastia

General disorders and administration site conditions

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

Uncommon: chest pain, fatigue

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

4.9 Overdose

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

Signes and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be

followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment

There is no specific antidote to MEDIKINET MR 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 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 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 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.

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 a intial 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 (Tmax) by approximately 1.5 hour. There is no difference in bioevailability of MEDIKINET MR given either a normal or high calorie breakfast. The plasma curves show similar exposure regarding rate and extend of absorption.
It is necessary to take MEDIKINET MR with or after breakfast. The food influence takes effect and shows a significant and relevant retardation. This justifies the posology to be taken with food. A recommendation in relation of type of food is not necessary. Administration without food can have a risk of dose dumping.

Sprinkle Administration:
The C_{max} T_{max} and AUC of the sprinkled contents of the MEDIKINET 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.

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

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

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

There is evidence that methylphenidate may be a teratogen in two species. Spina bifida and limb malformations have been reported in rabbits whilst in the rat, equivocal evidence of induction of abnormalities of the vertebrae was found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

in the capsule content:
Sugar sphere (sucrose, maize starch)
Methacrylic acid-ethylacrylate-copolymer (1:1)
Talc
Triethyl citrate
Poly(vinyl alcohol)
Macrogol 3350
Polysorbate 80
Sodium hydroxide
Sodium laurilsulfate
Simeticone emulsion
Silica colloidal anhydrous
Methylcellulose
Sorbic acid
Indigo carmine lacquer
Purified water

in the capsule shell:
Gelatin
Titanium dioxide (E 171)
Sodium laurilsulfate

additional in the capsule shell of MEDIKINET MR 10 mg and 20 mg:
Erythrosine (E 127)
Patent blue V (E 131)

additional in the capsule shell of MEDIKINET MR 30 mg and 40 mg:
Erythrosine (E 127)
Black iron oxide (E 172)
Indigo carmine (E 132)

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 the container

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

Not all pack sizes may be marketed.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MEDILINE LTD

CITY GATE, 22 G' BEN GURION ST. HERZLIA.

8. MARKETING AUTORISATION NUMBER

33165, 33166, 33180, 33790, 33819