SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

Medikinet MR 5 mg modified-release capsules, hard
Medikinet MR 10 mg modified-release capsules, hard
Medikinet MR 20 mg modified-release capsules, hard
Medikinet MR 30 mg modified-release capsules, hard
Medikinet MR 40 mg modified-release capsules, hard
Medikinet MR 50 mg modified-release capsules, hard
Medikinet MR 60 mg modified-release capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Medikinet MR 5 mg modified-release capsules, hard
Each modified-release capsule, hard contains 5 mg methylphenidate hydrochloride, equivalent to 4.35 mg methylphenidate.
Excipient with known effect:
Contains sugar: 63.57 mg – 72.71 mg sucrose/modified-release capsule, hard

Medikinet MR 10 mg modified-release capsules, hard
Each modified-release capsule, hard contains 10 mg methylphenidate hydrochloride, equivalent to 8.65 mg methylphenidate.
Excipient with known effect:
Contains sugar: 127.14 mg – 145.42 mg sucrose/modified-release capsule, hard

Medikinet MR 20 mg modified-release capsules, hard
Each modified-release capsule, hard contains 20 mg methylphenidate hydrochloride, equivalent to 17.30 mg methylphenidate.
Excipient with known effect:
Contains sugar: 114.65 mg – 131.13 mg sucrose/modified-release capsule, hard

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

Medikinet MR 40 mg modified-release capsules, hard
Each modified-release capsule, hard contains 40 mg methylphenidate hydrochloride, equivalent to 34.60 mg methylphenidate.
Excipient with known effect:
Contains sugar:92.80 mg – 106.14 mg sucrose/modified-release capsule, hard

Medikinet MR 50 mg modified-release capsules, hard
Each modified-release capsule, hard contains 50 mg methylphenidate hydrochloride, equivalent to 43.25 mg methylphenidate.
Excipient with known effect:
Contains sugar: 116.00 mg - 132.68 mg sucrose/modified-release capsule, hard

Medikinet MR 60 mg modified-release capsules, hard
Each modified-release capsule, hard contains 60 mg methylphenidate hydrochloride, equivalent to 51.90 mg methylphenidate.
Excipient with known effect:
Contains sugar: 139.20 mg - 159.22 mg sucrose/capsule

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medikinet MR 5 mg modified-release capsules, hard

White opaque capsule body/white opaque capsule cap (15.9 mm) containing white and blue pellets.

Medikinet MR 10 mg modified-release capsules, hard

White opaque capsule body/mauve opaque capsule cap (15.9 mm) containing white and blue pellets.

Medikinet MR 20 mg modified-release capsules, hard

Mauve opaque capsule body/mauve opaque capsule cap (15.9 mm) containing white and blue pellets.

Medikinet MR 30 mg modified-release capsules, hard

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

Medikinet MR 40 mg modified-release capsules, hard

Grey opaque capsule body/dark violet opaque capsule cap (18.0 mm) containing white and blue pellets.

Medikinet MR 50 mg modified-release capsules, hard

Violet opaque capsule body/dark violet opaque capsule cap (18.0 mm) containing white and blue pellets.

Medikinet MR 60 mg modified-release capsules, hard

Dark violet opaque capsule body/dark violet opaque capsule cap (19.4 mm) containing white and blue pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD) in Children 6 years or older and in adults with ADHD onset in childhood

Medikinet MR is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over and in adults with ADHD onset in childhood when remedial measures alone prove insufficient.

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

Special Diagnostic Considerations for ADHD in children

Diagnosis should be made according to current DSM criteria or the guidelines in International Classification of Diseases and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptoms.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

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

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

Special Diagnostic Considerations for ADHD in adults

Diagnosis should be made according to DSM criteria or the guidelines in International Classification of Diseases and should be based on a complete history and evaluation of the patient.

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adults with ADHD have symptom patterns characterized by, restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD. Diagnosis in adults should include a structured patient interview to determine current symptoms. The preexistence of childhood ADHD is required and has to be determined retrospectively (by patients' records or if not available by appropriate and structured instruments/interviews). Third-party corroboration is desirable and Medikinet MR should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment and diagnosis should include moderate or severe functional impairment in at least 2 settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

4.2 Posology and method of administration

Posology

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

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. In case of adults, only weight should be recorded (see sections 4.3 and 4.4).

Ongoing monitoring:

Growth (children), weight, 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 (children), weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;

- Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

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

Dose titration

General aspects:

- The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.
- Children should not take Medikinet MR too late in the morning as it may cause disturbances in sleep.
- For doses not realisable/practicable with this strength, other strengths of this medicinal product and other methylphenidate containing products are available.

Children

Careful dose titration is necessary at the start of treatment with methylphenidate. This is normally achieved using methylphenidate 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 medical practitioner considers that twice daily dosing is appropriate from the outset and twice daily treatment administration is impracticable.

For patients being treated with immediate release methylphenidate at a dose of 5 mg once daily and for whom once daily dosing in the morning does not provide a sufficient duration of action, the medical practitioner can switch to Medikinet MR treatment with an initial dose of 10 mg once daily.

Medikinet MR consists of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose). Hence Medikinet MR 10 mg yields an

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

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

If the effect of the medicinal product wears off too early in the evening, disturbed behaviour may recur.
A small dose of an immediate-release methylphenidate hydrochloride tablet late in the day may help to solve this problem. In that case, it could be considered that adequate symptom control might be achieved with a twice daily immediate-release methylphenidate regimen.
The pros and cons of a small evening dose of immediate-release methylphenidate versus disturbances in falling asleep should be considered.
Treatment should not continue with Medikinet MR if an additional late dose of immediate-release methylphenidate is required, unless it is known that the same extra dose was also required for a conventional immediate-release regimen at equivalent breakfast/lunchtime dose.
The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

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

Adults

Continuation of methylphenidate therapy
Adult patients who have shown clear benefit from treatment with Medikinet MR in childhood and/or adolescence may continue treatment with Medikinet MR into adulthood, initially at the same daily dose (mg/day). Whether or not a dose adjustment depending on efficacy and tolerability is necessary or possible must be reviewed regularly.

Adults new to Medikinet MR
Any treatment with Medikinet MR requires individual dose titration against efficacy and tolerability because individual response may vary substantially. Therefore, careful dose titration is required during initiation of treatment with Medikinet MR in adult patients with ADHD onset in childhood who have not previously been treated with methylphenidate or were treated with other methylphenidate formulations in the past.
Dose titration should be started at the lowest possible dose.
The recommended starting dose is 10 mg daily, which may be increased if necessary by weekly increments of 10 mg in the daily dose according to tolerability and degree of efficacy observed. The total daily dose should be given in two divided doses in the morning and at midday.

The aim of individual titration should be to find the lowest daily dose that achieves satisfactory symptom control.
Compared to children and adolescents, adult patients may require a higher daily dose, based on the patient's body weight.
The maximum daily dose is based on the patient's body weight and must not exceed 1 mg/kg body weight. Regardless of body weight, a maximum daily dose of 80 mg

methylphenidate hydrochloride should not be exceeded because limited experience with daily doses greater than 80 mg is available from clinical studies.

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

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

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

Children under 6 years of age
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.

Method of administration

Oral use.

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

<u>Children</u>
Medikinet MR should be given in the morning **with** or **after breakfast**.

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Glaucoma
- Phaeochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicinal products, due to risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the dysfunction of ion channels) and OT prolongation either congenital, familial or caused by medication. (See Section 4.4)
- Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke
- A history of pronounced anacidity of the stomach with a pH value above 5.5, in therapy with H_2 receptor blockers, proton pump inhibitors or in antacid therapy.
- Pregnancy and lactation (see Section 4.6)

4.4 Special warnings and precautions for use

Medikinet MR treatment is not indicated in all patients with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the patient's symptoms. When treatment of children is considered, assessment of the severity and chronicity of the child's symptoms should be related to the child's age (6 - 18 years).
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium free'.

Long-term use (more than 12 months)
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. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 for cardiovascular status, growth (children), weight, appetite, development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The medical practitioner who elects to use Medikinet MR for extended periods (over 12 months) should periodically re-evaluate the long term usefulness of the medicinal product for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that Medikinet MR is de-challenged at least once yearly to assess the patient's condition (for children

preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

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

Use in children under 6 years of age
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 dysrhythmia) 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 Medikinet MR in children and adolescents with ADHD showed that patients using Medikinet MR may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. Changes in diastolic and systolic blood pressure values were also observed in clinical trial data from adult ADHD patients.
The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate**.** See section 4.3 for conditions in which Medikinet MR treatment is contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of Medikinet MR is contraindicated in certain pre-existing cardiovascular disorders unless specialist cardiac advice has been obtained (see section 4.3).

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in patients with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and cardiovascular events
Misuse of stimulants of the central nervous system, such as Medikinet MR, 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 Medikinet MR, and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during Medikinet MR therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with Medikinet MR is not contraindicated in patients with hemiplegic cerebral palsy.

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

Psychiatric disorders
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, Medikinet MR should not be given.

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 Medikinet MR may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in patients without prior history of psychotic illness or mania can be caused by Medikinet MR at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for Medikinet MR and Medikinet MR, should be discontinued.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with Medikinet MR 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. Medical practitioners should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

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

Tics
Methylphenidate, as in Medikinet MR, 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 should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with Medikinet MR. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension
Methylphenidate, as in 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 Medikinet MR, 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 methylphenidate on final height and final weight are currently unknown and being studied.

Height (children), weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures
Methylphenidate, as in Medikinet MR, should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, Medikinet MR should be discontinued.

Abuse, misuse and diversion
Patients should be carefully monitored for the risk of diversion, misuse and abuse of Medikinet MR.

Medikinet MR should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of Medikinet MR 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, Medikinet MR or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal
Careful supervision is required during Medikinet MR 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 of Medikinet MR from abusive use since severe depression may occur.

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

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

Renal or hepatic insufficiency
There is no experience with the use of Medikinet MR in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with Medikinet MR is not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and platelet counts performed periodically. 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how Medikinet MR may affect plasma concentrations of concomitantly administered medicinal products. Therefore, caution is recommended at combining Medikinet MR with other medicinal products, especially those with a narrow therapeutic window.

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

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

Pharmacodynamic interactions

Anti-hypertensive medicinal products
Medikinet MR may decrease the effectiveness of active substances used to treat hypertension.

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

Because of possible hypertensive crisis, 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 active substances, including Medikinet MR. In case of very high alcohol concentrations the kinetic profile may change towards a more immediate release-like pattern. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics
There is a risk of sudden blood pressure 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.

Use with dopaminergic active substances

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Medikinet MR is contraindicated in pregnancy (see Section 4.3).

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 an increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Cases of neonatal cardio-respiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous case reports.

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

Breast-feeding
Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. Medikinet MR should not be used during breast feeding.

Fertility
No human data on the effect of methylphenidate on fertility are available. In animal studies, no clinically relevant effects on fertility were observed.

4.7 Effects on ability to drive and use machines

Medikinet MR can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision.
Patients on Medikinet MR experiencing these adverse effects should not drive and use machines.

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.

Frequency estimate:
very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1,000 to <1/100)

rare (≥ 1/10,000 to <1/1,000)
very rare (<1/10,000)
not known (cannot be estimated from the available data)

System Organ Class	Frequency					
	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis	gastroenteritis			
Blood and lymphatic system disorders					Anaemia[#], Leucopenia[#], Thrombocytopenia, Thrombocytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as Angioneurotic oedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, and Eruptions			
Metabolism and nutrition disorders*		Anorexia, Decreased appetite, Reduced weight and height gain during prolonged use in children*				
Psychiatric disorders*	Insomnia, Nervousness	Affect lability, Aggression*, Agitation*, Anxiety*, Depression*, Irritability, Abnormal behaviour, bruxism[∞] Panic attack ***	Psychotic disorders*, Auditory, visual and tactile hallucination*, Anger, Suicidal ideation*, Mood swings[#], Restlessness[#],	Mania*, Disorientation	Suicidal attempt (including completed suicide) *, Transient depressed mood*, Abnormal thinking, Apathy[#], Repetitive	Delusions*, Thought disturbances*, Confusional state· Dependence. cases of abuse and dependence have been described,

		stress***	Tearfulness, Tics*, Worsening of pre-existing tics of Tourette's syndrome*, Hypervigilance, Sleep disorder[#] tension***		behaviours, Over-focusing	more often with immediate release formulations, Logorrhoea, Tension[$], Bruxism[$]
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence	Sedation, Tremor[#], Akathisia***		Convulsions, Choreoathetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most cases, patients were also receiving other medicinal products, so the role of methylphenidate is unclear).	Cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion*, Migraine[#], Paraesthesia[$], Aphasia[$#] dysphemia
Eye disorders			Diplopia, Blurred vision[#]	Difficulties in visual accom-modation, Mydriasis, Visual disturbance		Dry eye[$], Ocular hypertension
Cardiac disorders*	Palpitations	Dysrhythmia, Tachycardia	Chest pain	Angina pectoris	Cardiac arrest; Myocardial infarction	Supraventricular tachycardia, Bradycardia, Ventricular extrasystoles, Extrasystoles, Cardiac discomfort[$]
Vascular disorders*		Hypertension			Cerebral arteritis and/or occlusion, Peripheral coldness, Raynaud's phenomenon	Hot flush[$], Flushing[$]
Respiratory,		Cough,	Dyspnoea			Oropharynge

thoracic and mediastinal disorders		Pharyngolaryngeal pain				al pain[$], Epistaxis[$],
Gastrointestinal disorders		Abdominal pain, Diarrhoea, Nausea, Stomach discomfort, Vomiting - These usually occur at the beginning of treatment and may be alleviated by concomitant food intake, Dry mouth dyspepsia,*** toothache***	Constipation			Retching[$]
Hepatobiliary disorders					Abnormal liver function, including hepatic coma	
Skin and subcutaneous tissue disorders		Alopecia, Pruritis, Rash, Urticaria, Hyperhidrosis **	Angioedema, Bullous conditions, Exfoliative conditions	Macular rash; Erythema	Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption	Dry skin
Musculoskeletal and connective tissue disorders		Arthralgia	Myalgia, Muscle twitching muscle tightness***		Muscle cramps	Trismus[∞]
Renal and urinary disorders			Haematuria			Incontinence
Reproductive system and breast disorders				Gynaecomastia, Menstruation disorder[$], Impairment of libido[$]		Erectile dysfunction, Priapism, Erection increased and prolonged erection, Breast pain[$]
General disorders and administration site conditions		Pyrexia,	Fatigue Thirst***		Sudden cardiac death*	Hyperpyrexia, Disturbance in attention[$], Influenza like illness[$], Asthenia[$], Thirst[$]
Investigations		Changes in blood pressure and heart rate (usually an increase)*,	Cardiac murmur*, Hepatic enzyme increased		Blood alkaline phosphatase increased, Blood	Blood thyroid stimulating hormone

		Weight decreased*			bilirubin increased, Platelet count decreased, White blood cell count abnormal	increased[$]
Social circumstances						Partner stress[$], Family stress[$]
Ear and labyrinth disorders						Tinnitus[$]

*see section 4.4
** ADR from clinical trials in adult patients that was reported with a higher frequency than in children and adolescents
*** ADR from clinical trials in adult patients that were not reported in children and adolescents

[#] Frequency derived from data and experiences from children and adolescents but may be higher in adults due to results of clinical trials.

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

[∞] Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies.)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important.

It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked

to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug**

Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Additionally, suspected adverse reactions can be reported to the Holder of Certificate of

Registration via pv@mcpharma.co.za.

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 dysrhymias, hypertension, mydriasis and dryness of mucous membranes.

Treatment
There is no specific antidote to Medikinet MR overdose.
Treatment consists of appropriate symptomatic and supportive measures.
The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Measures to detoxify the gut include administration of activated charcoal and a cathartic.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics (A.1.2): psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics
ATC Code: N06BA04

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

Clinical efficacy and safety
The efficacy and safety of Medikinet MR in adult ADHD patients was investigated in two randomised, double-blind, placebo-controlled clinical trials. In the EMMA study, 363 patients were treated for 24 weeks; in the QUMEA study, 162 patients were treated for 20 weeks (8-week double-blind phase followed by a 12-week open-label phase). The daily dose was individually titrated at weekly intervals based on efficacy and tolerability. The primary end point was the WRI (Wender-Reimherr-Interview = WRAADS) total score at week 24 (EMMA) or week 8 (QUMEA).
The mean daily methylphenidate dose at end point was 0.55 mg/kg in the EMMA study and 0.9 mg/kg in the QUMEA study. In the EMMA study, the WRI total score change from baseline to week 24 was -18.88 on verum compared to -13.99 on placebo, corresponding to an effect size of 0.39, 95% CI (0.18, 0.63, for effect size), p=0.002. In the QUMEA study, the WRI total score change from baseline to week 8 was -13.2 on verum compared to -6.2 on placebo, corresponding to an effect size of 0.54, 95% CI (0.22, 0.85, for effect size), p=0.0001. A greater effect size was achieved when administering a higher average dose (0.9 mg/kg body weight), as was the case in the QUMEA study. The clinical studies yielded only limited experience with daily doses of over 80 mg, since only 2 patients were treated with 120 mg/day.
Treatment response was defined as a ≥30% reduction in WRI total score from baseline to end point. In the EMMA trial, the response rate at week 24 was 53% (n=128) in the

verum group vs. 37% (n=44) in the placebo group (p=0.0051). In the QUMEA trial, the response rate was 49% (n=41) in the verum group vs. 18% (n=14) in the placebo group (p<0.0001).
Medikinet MR was also studied in a further randomised, double-blind, placebo-controlled clinical trial (COMPAS study) in 433 adult patients with ADHD.
The patients received either cognitive behavioural group psychotherapy or individual clinical manage-ment in addition to daily doses of Medikinet MR or placebo.
Treatment duration was 52 weeks. The primary outcome was the change in the ADHD Index of the Conners Adult ADHD Rating Scale (CAARS-O:L) from baseline to the end of the first 12 weeks of treatment.
The average daily dose (SD) in 179 patients treated with Medikinet MR was 48.8 (20.2) mg. ADHD symptoms markedly decreased during treatment with Medikinet MR (n=210; adjusted mean ADHD index score, 16.2; ES = −0.81) as compared to placebo (n=209; adjusted mean ADHD index score, 17.9; ES = −0.50). The difference was statistically significant (ADHD Index score difference for Medi-kinet MR vs. placebo – 1.7; 97.5% CI, −3.0 vs. −0.4; 95% CI, −2.8 vs. −0.6; p=0.003). After 1 year, treatment effects remained essentially stable.
In conclusion, the COMPAS trial showed that in adults, psychological interventions under controlled conditions rendered a superior treatment outcome (over 52 weeks) when combined with Medikinet MR as compared to a combination with placebo.

5.2 Pharmacokinetic properties

Absorption
Methylphenidate 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.
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 the absorption (t_{max}) of methylphenidate by approximately 1.5 hour. There is no difference in bioavailability of Medikinet MR given either a normal or high calorie breakfast. The plasma curves show similar exposure regarding rate and extend of absorption.
It is necessary to take Medikinet MR with or after breakfast. The food influence takes effect and shows a significant and relevant retardation. Therefore, Medikinet MR should be taken with food or after food.

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.

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

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

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

The renal elimination of ritalinic acid may decrease in the case of impaired renal function.
The bulk of the dose is excreted in the urine as 2-phenyl-2-piperidyl acetic acid (PPAA, 60-86%).

Pharmacokinetics in special patient groups

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

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

Renal impairment
Elimination data from patients with normal renal function suggest that renal excretion of the unchanged methylphenidate would hardly be diminished at all in the presence of impaired renal function. However, renal excretion of PPAA may be reduced.

5.3 Preclinical safety data

Carcinogenicity
In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

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

Pregnancy-embryonal/foetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Sodium laurilsulfate
Purified water

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

additional in the capsule shell of Medikinet MR 30 mg/- 40 mg/-50 mg /- 60 mg:
Erythrosine (E 127)
Iron oxide black (E 172)
Indigo carmine (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of the container

Medikinet MR 5 mg:

Boxes of 20, 30 or 50 modified-release capsules, hard in PVC/PVdC blisters heat sealed to aluminium foil.

Medikinet MR 10 mg/- 20 mg/-30 mg /- 40 mg:

Boxes of 20, 28, 30 or 50 modified-release capsules, hard in PVC/PVdC blisters heat sealed to aluminium foil.

Medikinet MR 50 mg /- 60 mg:

Boxes of 20, 28, 30, 40 modified-release capsules, hard in PVC/PVdC blisters heat sealed to aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MC Pharma (Pty) Ltd

Plot 87, 62 Constantia Avenue

Mnandi

Centurion

0157

Republic of South Africa

e-mail: pharmacist@mcpharma.co.za

8. REGISTRATION NUMBER(S)

Medikinet MR 5 mg: 51/1.2/1088

Medikinet MR 10 mg: 51/1.2/1089

Medikinet MR 20 mg: 51/1.2/1090

Medikinet MR 30 mg: 51/1.2/1091

Medikinet MR 40 mg: 51/1.2/1092

Medikinet MR 50 mg: 51/1.2/1093

Medikinet MR 60 mg: 51/1.2/1094

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

24 August 2021

10. DATE OF REVISION OF THE TEXT

29 November 2021