APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

METHYCAP 10 mg LA Modified release capsules

METHYCAP 20 mg LA Modified release capsules

METHYCAP 30 mg LA Modified release capsules

METHYCAP 40 mg LA Modified release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METHYCAP 10 mg LA: Each capsule contains 10 mg methylphenidate hydrochloride. Contains sugar: 59,7 mg sucrose.

METHYCAP 20 mg LA: Each capsule contains 20 mg methylphenidate hydrochloride. Contains sugar:119,5 mg sucrose.

METHYCAP 30 mg LA: Each capsule contains 30 mg methylphenidate hydrochloride. Contains sugar: 179,2 mg sucrose.

METHYCAP 40 mg LA: Each capsule contains 40 mg methylphenidate hydrochloride. Contains sugar: 238,9 mg sucrose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Modified release hard capsules

METHYCAP 10 mg LA: Hard gelatin capsule size 2, with a dark yellow opaque cap and a white opaque body, imprinted with “RUB” in red ink on the cap and “M10” in red ink on the body, containing white and whitish pellets. Capsule length: 18 mm.

METHYCAP 20 mg LA: Hard gelatin capsule size 2, white opaque capsule, imprinted with “RUB” in red ink on the cap and “M20” in red ink on the body, containing white and whitish pellets. Capsule length: 18 mm.

METHYCAP 30 mg LA: Hard gelatin capsule size 2, ivory opaque capsule, imprinted with “RUB” in red ink on the cap and “M30” in red ink on the body, containing white and whitish pellets. Capsule length: 18 mm.

METHYCAP 40 mg LA: Hard gelatin capsule size 1, dark yellow opaque, imprinted with “RUB” in red ink on the cap and “M40” in red ink on the body, containing white and whitish pellets. Capsule length: 20 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METHYCAP LA is indicated for attention deficit hyperactivity disorder (ADHD) in children aged 6 years or older, and in adults with ADHD onset in childhood.

ADHD diagnosis should be made according to current DSM criteria or the guidance from International Classification of Diseases (ICD).

4.2 Posology and method of administration

Posology

The dosage of METHYCAP LA should be individualised according to the patient’s clinical needs and responses.

METHYCAP LA should be started at a low dose, with increments at weekly intervals.

Daily doses above 60 mg are not recommended for the treatment of ADHD in children. Effective doses in adults may vary, and range from 40 – 80 mg per day.

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults.

METHYCAP LA should be discontinued if improvement is not observed after appropriate dosage adjustment over a one-month period.

METHYCAP LA should be discontinued if paradoxical aggravation of symptoms or other adverse effects occur.

Pre-treatment screening

Patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular dysrhythmia and psychiatric disorders prior to treatment initiation of METHYCAP LA (see sections 4.3 and 4.4).

Periodic assessment of the treatment in ADHD

METHYCAP LA treatment should not and need not be indefinite and should be periodically discontinued to assess the patient's condition. Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

When used in children with ADHD, METHYCAP LA can usually be discontinued after puberty.

Paediatric population

Children and adolescents (6 years and older)

METHYCAP LA is for oral administration once daily, in the morning. The recommended starting dose is 20 mg. When, in the judgement of the clinician, a lower initial dose is appropriate, patients may begin treatment with METHYCAP 10 mg LA.

Daily dosage above 60 mg is not recommended.

Adults

The individualised dose of METHYCAP LA is administered once daily in the morning.

The recommended starting dose of METHYCAP LA in patients who are new to, or not currently taking methylphenidate, is 20 mg once daily.

In patients currently taking methylphenidate, treatment may be continued with the same daily dose. If the patient was previously treated with an immediate release formulation, a conversion to an appropriate recommended dose of METHYCAP LA should be made (see below subsection Switching patients to METHYCAP LA).

A maximum dose of 80 mg should not be exceeded.

Switching patients to METHYCAP LA

The recommended dose of METHYCAP LA should be equal to the total daily dose of an immediate release formulation not exceeding a total of 60 mg in children and 80 mg in adults. An example in patients being switched from the immediate-released formulation is provided below.

Recommended daily dose when switching patients to METHYCAP LA

Previous Methylphenidate dose	**Recommended METHYCAP LA dose**
5 mg methylphenidate twice daily	10 mg once daily
10 mg methylphenidate twice daily	20 mg once daily
15 mg methylphenidate twice daily	30 mg once daily
20 mg methylphenidate twice daily	40 mg once daily

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. METHYCAP LA dosage may be adjusted at weekly intervals in 10 mg increments for children and in 20 mg increments for adults.

Special populations

Renal impairment

No studies have been performed in renally impaired patients.

Hepatic impairment

No studies have been performed in hepatically impaired patients.

Elderly patients

No studies have been performed in patients over the age of 60.

Method of administration

General recommendations

METHYCAP LA is for oral administration once daily, in the morning. METHYCAP LA capsules may be taken/administered with or without food. They should be swallowed whole, or alternatively the contents of the capsule can be sprinkled over a small amount of food (refer to specific instructions below). The granules must be swallowed whole and not chewed or crushed.

METHYCAP LA capsules and/or their contents should not be crushed or chewed.

When METHYCAP LA is administered/taken by sprinkling capsule contents on food

The capsules may be carefully opened and the beads sprinkled over soft food.

The food should not be warm because this could affect the modified-release properties of this formulation.

The mixture of medicine and food should be consumed immediately in its entirety. This soft food mixture should not be chewed but swallowed only.

The medicine and food mixture should not be stored for future use.

METHYCAP LA, administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of methylphenidate administered twice daily.

Missed dose

Doctors should advise patients who forget to take METHYCAP LA to take it as soon as they remember in the morning, failing which, the normal dose should be taken the next day. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

METHYCAP LA is contrainidicated in the following:

- hypersensitivity to methylphenidate or to any of the excipients of METHYCAP LA (see section 6.1)
- anxiety, tension, agitation
- family history or diagnosis of Tourette's Syndrome
- 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 1) Bipolar (affective) disorder (that is not well controlled)
- glaucoma
- phaeochromocytoma
- pre-existing cardiovascular disorders, including hypertension, angina, arterial occlusive disease; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias, channelopathies (disorders caused by the dysfunction of ion channels) and QT prolongation either congenital, familial or caused by medication (see section 4.4)
- pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders

- during treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 2 weeks of discontinuing those medicines, due to risk of hypertensive crisis (see section 4.5)
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

General

METHYCAP LA should not be used for the prevention or treatment of normal fatigue states.

METHYCAP LA is not indicated in all cases of Attention-deficit/Hyperactivity disorder and should be considered only after detailed history-taking and evaluation. The decision to prescribe METHYCAP LA should depend on a thorough assessment of the severity and chronicity of symptoms and, in paediatric patients, their appropriateness to the child's age and not simply on the presence of one or more abnormal behavioural characteristics.

METHYCAP LA should not be used for the treatment of attention-deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

Chronic abuse of METHYCAP LA can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur. Abuse of METHYCAP LA may prove a problem in predisposed patients e.g. in emotionally unstable individuals or those with a history of drug dependence or alcoholism.
METHYCAP LA should therefore be used only under medical supervision. Clinical data indicate that children given methylphenidate are not more likely to abuse drugs than adolescents or adults.

Cardiovascular

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Sudden death has been reported in association with the use of methylphenidate at usual doses in patients with pre-existing structural cardiac abnormalities or other serious heart problems. No causal relationship with METHYCAP LA has been established since some of these conditions alone may carry an increased risk of sudden death. METHYCAP LA generally should not be used in patients with known structural cardiac abnormalities or other serious cardiac disorders that may increase the risk of sudden death due to its sympathomimetic effects. Before initiating METHYCAP LA treatment, patients should be assessed for pre-existing cardiovascular disorders such as a congenital long QT syndrome, or a family history of sudden death and ventricular dysrhythmia (see section 4.2).

Misuse and Cardiovascular Events

Misuse of METHYCAP LA, may be associated with sudden death and other serious cardiovascular adverse events.

Cardiovascular conditions

METHYCAP LA is contraindicated in patients with hypertension. METHYCAP LA increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension and severe cardiovascular disorders (see section 4.3).

Monitoring of blood pressure at appropriate intervals should be undertaken in all patients taking METHYCAP LA. A prompt cardiac evaluation should be undertaken should a patient develop symptoms suggestive of cardiac disease during while taking METHYCAP LA.

Cerebrovascular conditions

Patients with pre-existing central nervous system (CNS) abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with METHYCAP LA.

Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with METHYCAP LA (see above, paragraph on Cardiovascular Conditions and section 4.5).

Cerebral vasculitis appears to be 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 METHYCAP LA and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during METHYCAP LA therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with METHYCAP LA 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 METHYCAP LA. Prior to initiating treatment with METHYCAP LA, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section 4.2). Treatment of ADHD with METHYCAP LA should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered.

In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, METHYCAP LA should not be given to patients unless the benefit outweighs the potential risk.

Patients diagnosed with or have history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder should not be treated with METHYCAP LA.

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 METHYCAP LA at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for METHYCAP LA and discontinuation of treatment may be appropriate.

Aggressive behaviour

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour or hostility may occur during METHYCAP LA therapy. However, patients with ADHD may experience aggression as part of their medical condition. Therefore, a causal association with treatment may be difficult to assess. Medical practitioners should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

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

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see section 4.8). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of METHYCAP LA for ADHD treatment. METHYCAP LA is contraindicated in case of diagnosis or family history of Tourette's syndrome (see section 4.3). Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension

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

Forms of bipolar disorder

Particular care should be taken in using METHYCAP LA to treat ADHD in patients with co-morbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with co- morbid 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.

If a patient is diagnosed or have a history of severe and episodic (Type 1) Bipolar (affective) disorder, that is not well controlled, treatment with METHYCAP LA is not recommended.

Serotonin syndrome

Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of METHYCAP LA and serotonergic medicines is not recommended as this may lead to the development of serotonin syndrome. The symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Prompt recognition of these symptoms is important so that treatment with METHYCAP LA and serotonergic medicines can be immediately discontinued and appropriate treatment instituted (see section 4.5).

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both paediatric and adult patients. Priapism generally developed after some time on the medicine, often subsequent to an increase in dose. Priapism has also been reported during a period of medicine withdrawal (medicine holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Growth retardation

Reduced weight gain and slight growth retardation have been reported with the long-term use of METHYCAP LA (see section 4.8). Growth, weight, and appetite should be monitored at least 6 monthly during treatment with METHYCAP LA with maintenance of a growth chart. Patients who are

not gaining height or weight as expected or are losing weight may need to have their treatment interrupted and adjusted.

Haematological effects

The long-term safety and efficacy profiles of METHYCAP LA are not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. In the event of haematological disorders appropriate medical intervention should be considered (see section 4.8).

Seizures

METHYCAP LA should be used with caution in patients with epilepsy as clinical experience has shown that it can cause an increase in seizure frequency. Methylphenidate may lower the convulsive threshold in patients 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, METHYCAP LA should be discontinued.

Medicine abuse and dependence

METHYCAP LA 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 METHYCAP LA can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially with 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 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 dependence or alcoholism, because they 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 METHYCAP LA 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.

Excipients with known effect

METHYCAP LA capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take METHYCAP LA capsules.

Paediatric population

METHYCAP LA is not indicated in children younger than 6 years.

Treatment with METHYCAP LA is not indicated in all cases of Attention-Deficit/Hyperactivity disorder and should be considered only after detailed history-taking and evaluation. The decision to prescribe METHYCAP LA should depend on the medical practitioner assessment of the chronicity and severity of the child's symptoms and, their appropriateness to the child's age. Prescription should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with METHYCAP LA is not indicated.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

Anti-hypertensive medicines

The effectiveness of medicines used to treat hypertension may be decreased with concomitant use of METHYCAP LA.

Use with medicines that elevate blood pressure

METHYCAP LA should be used with caution in patients being treated with medicines that elevate blood pressure (see paragraph on Cerebrovascular Conditions under section 4.4). METHYCAP LA is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors due to the risk of hypertensive crisis (see section 4.3).

Use with alcohol

Alcohol may exacerbate the central nervous system adverse reactions of METHYCAP LA. Alcohol can also affect the coating of the capsule contents causing accelerated release or dose dumping, potentially leading to toxicity. It is advisable for patients to abstain from alcohol during treatment.

Use with dopaminergic medicines

As an inhibitor of dopamine reuptake, METHYCAP LA may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g. haloperidol). The co-administration of METHYCAP LA with antipsychotics is not recommended because of the counteracting mechanism of action.

Use with anaesthetics

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

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

Serious adverse events including sudden death may occur in concomitant use with clonidine or dexmedetomidine, although no causality for the combination has been established.

Use with serotonergic medicine

Concomitant use of METHYCAP LA and serotonergic medicine is not recommended as this may lead to the development of serotonin syndrome (see section 4.4).
Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic interactions

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered medicine. Therefore, caution is recommended at combining methylphenidate with other medicine, 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 METHYCAP LA pharmacokinetics.

Conversely, the d- and l- enantiomers of methylphenidate as in METHYCAP LA did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Methylphenidate co-administration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports suggested a potential interaction of methylphenidate as in METHYCAP LA with warfarin, some anticonvulsants (e.g. phenobarbital, phenytoin, primidone) and tricyclic antidepressants, however pharmacokinetic interactions were not confirmed when explored at higher sample sizes. The dosage of these medicines might have to be reduced.

Other specific medicine-medicine interaction studies with methylphenidate have not been performed *in vivo*.

When starting and stopping treatment with METHYCAP LA, it may be necessary to adjust the dosage of these medicine already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Medicine/Laboratory test

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

4.6 Fertility, pregnancy and lactation

Pregnancy

METHYCAP LA is contraindicated in pregnancy and lactation as safety has not been demonstrated (see section 4.3).

Breastfeeding

Mothers taking METHYCAP LA should not breastfeed their infants.

Fertility

No human data on the effect of methylphenidate on fertility are available.

4.7 Effects on ability to drive and use machines

METHYCAP LA may cause dizziness, drowsiness, blurred vision, hallucinations, or other CNS side-effects (see section 4.8). It may have a moderate influence on the ability to drive and use machines. Patients experiencing such side-effects should refrain from driving, operating machines or engaging in other potentially hazardous activities.

4.8 Undesirable effects

a) Summary of the safety profile

Nervousness and insomnia are very common adverse reactions. These usually occur at the beginning of treatment and may be reduced by decreasing the dose and omitting the METHYCAP LA in the afternoon or evening.

Decreased appetite is very common.

Abdominal pain, nausea and vomiting are common to very common.

Reports of neuroleptic malignant syndrome (NMS) have been received. In most of these reports, patients were also receiving other medications. It is uncertain what role methylphenidate played in these cases.

b) Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Nasopharyngitis
	Less frequent	Gastroenteritis
Blood and lymphatic system disorders	Less frequent	Leucopenia, thrombocytopenia, anaemia
	Frequency unknown	Pancytopenia, epistaxis

Immune system disorders	Less frequent	Hypersensitivity reactions, such as auricular swelling, including angioedema and anaphylaxis
Metabolism and nutrition disorders	Frequent	Decreased appetite
	Less frequent	Anorexia, reduced weight and height gain during prolonged use in children
Psychiatric disorders	Frequent	Nervousness, insomnia, affect lability, aggression, irritability, abnormal behaviour, libido decreased, panic attack, stress, bruxism, anxiety, restlessness, sleep disorder, agitation
	Less frequent	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood, anger, tearfulness, mood altered, mood swings, hypervigilance, tension, mania, disorientation, abnormal thinking, apathy, repetitive behaviours, over-focusing, suicidal ideation or attempt (including completed suicide), libido disorder, apathy, confusional state, dependence, cases of abuse and dependence
	Frequency unknown	Delusions, thought disturbances, logorrhoea

Nervous system disorders	Frequent	Dyskinesia, tremor, headache, drowsiness, dizziness, psychomotor hyperactivity, somnolence
	Less frequent	Convulsions, choreo-athetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents, sedation, akathisia, dysphemia, reversible ischaemic neurological deficit
	Frequency unknown	Migraine, cerebral arteritis, cerebral occlusion, grand mal convulsions
Eye disorders	Less frequent	Blurred vision, difficulties in visual accommodation, mydriasis, visual disturbances
	Frequency unknown	Diplopia
Cardiac disorders	Frequent	Dysrhythmia, tachycardia palpitations
	Less frequent	Chest pain, angina pectoris, cardiac arrest, myocardial infarction
	Frequency unknown	Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders	Frequent Less frequent	Hypertension, peripheral coldness Cerebral arteritis and or occlusion, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, pharyngolaryngeal pain, dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Nausea, dry mouth, abdominal pain, diarrhoea, stomach discomfort, vomiting, dyspepsia, toothache Constipation
Hepatobiliary disorders	Less frequent	Hepatic enzyme elevations, abnormal liver functions, including hepatic coma
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash, pruritus, urticaria, fever, scalp hair loss (alopecia), hyperhidrosis Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme, angioneurotic oedema, bullous conditions, exfoliate conditions, macular rash, erythema fixed drug eruption Angioedema

Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Arthralgia Muscle cramps, muscle tightness, myalgia, muscle twitching Trismus
Renal and urinary disorders	Less frequent Frequency unknown	Haematuria Incontinence
Reproductive system and breast disorders	Less frequent Frequency unknown	Gynaecomastia Priapism, erectile dysfunction, erection increased and prolonged erection
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Feeling jittery, pyrexia, thirst, growth retardation during prolonged use in children, fatigue Chest pain, sudden cardiac death Chest discomfort, hyperpyrexia
Investigations	Frequent Less frequent	Weight decreased, changes in blood pressure and heart rate (usually an increase) Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal, cardiac murmur, hepatic enzyme increased

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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac dysrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Management of overdose

When treating overdose, the healthcare provider should bear in mind that a second release of methylphenidate from METHYCAP LA (methylphenidate hydrochloride modified-release capsules) occurs at approximately four hours after administration.

There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events e.g. hypertensive crisis, cardiac dysrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the healthcare provider should consult a certified Poison Control Centre or current toxicological publication.

Supportive measures include protection of the patient against self-injury and against external stimuli that would exacerbate the overstimulation already present. If the overdose is oral and the patient is conscious, administration of activated charcoal is recommended.

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

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdosage of METHYCAP LA has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychostimulants

ATC code: NO6B AO4

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Methylphenidate is a racemate, consisting of a 1:1 mixture of d-methylphenidate and l-methylphenidate.

Methylphenidate is a central nervous system stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood, but its stimulant effects are thought to be due to inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine. The mechanism by which methylphenidate 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.

The effect of treatment with 40 mg dexmethylphenidate hydrochloride, the pharmacologically active d-enantiomer of methylphenidate, on QT/QTc interval was evaluated in a study in 75 healthy adult volunteers. The maximum mean prolongation of QTcF intervals was < 5 millisecond (ms), and the upper limit of the 90 % confidence interval was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and no exposure response relationship was evident.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of methylphenidate hydrochloride (modified-release capsules) to children diagnosed with ADHD and adults, methylphenidate plasma concentration-time profiles show a bi-modal profile (i.e. two distinct peaks approximately four hours apart). The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for methylphenidate modified release given once a day compared to methylphenidate tablets given twice a day. Methylphenidate hydrochloride may be administered with or without food. There were no differences in the bioavailability of methylphenidate modified release when administered with either a high fat breakfast or applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the capsule, the contents may be sprinkled on soft food and administered (see section 4.2).

Distribution

In the blood, methylphenidate and its metabolites are distributed in the plasma (57 %) and in the erythrocytes (43 %). Methylphenidate and its metabolites have a low plasma protein-binding (10 to 33 %).

The apparent distribution volume has been calculated as 13,1 L/kg after an oral dose; the volume of distribution after intravenous dose (Vss) is 2,23 L/kg for the racemate in healthy adult volunteers. The volume of distribution was 2,65 ± 1,11 L/kg for dextromethylphenidate (d-MPH) and 1,80 ± 0,91 L/kg for levomethylphenidate (l-MPH).

Methylphenidate is excreted in breast milk.

Biotransformation

Peak plasma concentrations of PPAA (ritalinic acid) are attained approximately 2 hours after administration of methylphenidate and are 30 to 50 times higher than those of the unchanged substance. The half-life of PPAA is roughly twice as long as that of methylphenidate, and the mean systemic clearance is 0,17 L/h/kg.

Elimination

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours, and the systemic clearance is 0,40 ± 0,12 L/h/kg for d-MPH and 0,73 ± 0,28 L/h/kg for l-MPH. After oral administration 78 to 97 % of the dose is excreted in the urine and 1 to 3 % in the faeces in the form of metabolites within 48 to 96 hours. Unchanged methylphenidate appears in the urine only in small quantities (< 1 %). The bulk of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (PPAA, 60 to 86 %).

Pharmacokinetics in special patient groups

Paediatrics

There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and healthy adult volunteers.

Renal failure

Renal excretion of the unchanged methylphenidate is hardly diminished at all in the presence of impaired renal function; however, renal excretion of PPAA is reduced.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Ammonio methacrylate copolymer

Methacrylic acid-methyl methacrylate copolymer,

Povidone

Sugar spheres (sucrose and maize starch)

Talc

Triethyl citrate

Hard gelatin capsule size 2 (10 mg, 30 mg and 40 mg)

Gelatin

Titanium dioxide

Yellow iron oxide

Hard gelatin capsule size 2 (20 mg)

Gelatin

Titanium dioxide

Red printing ink

Potassium hydroxide

Propylene glycol

Red iron oxide

Shellac glaze

Strong ammonia solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C and protect from moisture.

Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

Peelable child-resistant blisters (Aclar/PVC/Al/PET) cross-perforated.

Each blister contains 10 capsules, 3 blister strips per outer carton (30 capsules).

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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Silverwood Close

Westlake, 7945, Cape Town

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or 0860-PHARMA (742 762)

8. REGISTRATION NUMBERS

METHYCAP 10 mg LA: 57/1.2/0792

METHYCAP 20 mg LA: 57/1.2/0793

METHYCAP 30 mg LA: 57/1.2/0794

METHYCAP 40 mg LA: 57/1.2/0795

9. DATE OF FIRST AUTHORISATION

02 September 2025