SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

Methylphenidate 10 LA Biotech, 10 mg modified-release hard capsules

Methylphenidate 20 LA Biotech, 20 mg modified-release hard capsules

Methylphenidate 30 LA Biotech, 30 mg modified-release hard capsules

Methylphenidate 40 LA Biotech, 40 mg modified-release hard capsules

Methylphenidate 60 LA Biotech, 60 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylphenidate 10 LA Biotech: Each modified-release capsule contains 10 mg methylphenidate hydrochloride (equivalent to 8,65 mg methylphenidate).

Methylphenidate 20 LA Biotech: Each modified-release capsule contains 20 mg methylphenidate hydrochloride (equivalent to 17,3 mg methylphenidate).

Methylphenidate 30 LA Biotech: Each modified-release capsule contains 30 mg methylphenidate hydrochloride (equivalent to 25,95 mg methylphenidate).

Methylphenidate 40 LA Biotech: Each modified-release capsule contains 40 mg methylphenidate hydrochloride (equivalent to 34,6 mg methylphenidate).

Methylphenidate 60 LA Biotech: Each modified-release capsule contains 60 mg methylphenidate hydrochloride (equivalent to 51,9 mg methylphenidate).

Excipient(s) with known effect:

Each modified-release capsule contains 10, 20, 30, 40 or 60 mg methylphenidate hydrochloride, respectively

Contains sugar (sucrose):

Each capsule of 10 mg contains 59,7 mg sucrose.

Each capsule of 20 mg contains 119,5 mg sucrose.

Each capsule of 30 mg contains 179,2 mg sucrose.

Each capsule of 40 mg contains 238,9 mg sucrose.

Each capsule of 60 mg contains 358,4 mg sucrose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsules, hard.

Methylphenidate 10 LA Biotech modified-release hard capsules:

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.

Methylphenidate 20 LA Biotech modified-release hard capsules:

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.

Methylphenidate 30 LA Biotech modified-release hard capsules:

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.

Methylphenidate 40 LA Biotech modified-release hard capsules:

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.

Methylphenidate 60 LA Biotech modified-release hard capsules:

Hard gelatin capsule size 0, with a dark yellow opaque cap and an ivory opaque body, imprinted with “RUB” in red ink on the cap and “M60” in red ink on the body, containing white and whitish pellets. Capsule length: 22 mm.

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

Methylphenidate LA Biotech 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 medical practitioner 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 Diagnostic and Statistical Manual of Mental Disorders (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.

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

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of Methylphenidate LA Biotech should always be 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 aetiology of this syndrome is unknown, and there is no single diagnostic test. Adults with ADHD have symptom patterns characterised 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 pre-existence 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 Methylphenidate LA Biotech 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 medical practitioner 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 Methylphenidate LA Biotech too late in the morning as it may cause disturbances in sleep.
- For doses not realisable/practicable with this strength, other strengths of this medicine and other methylphenidate containing products are available.

Children

Careful dose titration is necessary at the start of treatment with Methylphenidate LA Biotech. 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. Methylphenidate 10 LA Biotech 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 not 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 Methylphenidate LA Biotech treatment with an initial dose of 10 mg once daily.

Methylphenidate LA Biotech consists of an immediate-release component (50 % of the dose) and a modified-release component (50 % of the dose). Hence Methylphenidate LA Biotech 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 Methylphenidate LA Biotech 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 Methylphenidate LA Biotech.

If the effect of the medicine 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 Methylphenidate LA Biotech 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 Methylphenidate LA Biotech in childhood and/or adolescence may continue treatment with Methylphenidate LA Biotech 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 Methylphenidate LA Biotech

Any treatment with Methylphenidate LA Biotech 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 Methylphenidate LA Biotech 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 Methylphenidate LA Biotech has not been systematically evaluated in controlled trials. Methylphenidate LA Biotech treatment should not and need not, be indefinite. Methylphenidate LA Biotech treatment can usually be discontinued during or after puberty, when used in children with ADHD. The medical practitioner who elects to use Methylphenidate LA Biotech for extended periods (over 12 months) should periodically re-evaluate the long term usefulness of the medicine for the individual patient with trial periods off medication to assess the patient’s functioning without pharmacotherapy. It is recommended that Methylphenidate LA Biotech 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 medicine 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.

Special populations

Elderly

Methylphenidate LA Biotech should not be used in the elderly. Safety and efficacy have not been established in patients older than 60 years of age.

Children under 6 years of age

Methylphenidate LA Biotech 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.

Methylphenidate LA Biotech can be taken with or without food.

Children

Methylphenidate LA Biotech should be given in the morning with or without food.

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

- Known hypersensitivity to methylphenidate or to any of the excipients of Methylphenidate LA Biotech 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 medicines, 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, 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
- 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

Methylphenidate treatment is not indicated in all patients with ADHD and the decision to use Methylphenidate LA Biotech must be based on a very thorough assessment of the severity and chronicity of the 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).

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

The safety and efficacy of long-term use of Methylphenidate LA Biotech has not been systematically evaluated in controlled trials. Methylphenidate LA Biotech 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 Methylphenidate LA Biotech for extended periods (over 12 months) should periodically re-evaluate the long term usefulness of the medicine for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that Methylphenidate LA Biotech 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 medicine is either temporarily or permanently discontinued.

Use in the elderly

Methylphenidate LA Biotech must not be used in the elderly. Safety and efficacy has not been evaluated in ADHD in patients older than 60 years.

Use in children under 6 years of age

Methylphenidate LA Biotech 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 stimulants 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, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during Methylphenidate LA Biotech treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using Methylphenidate LA Biotech may frequently 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 adults 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).

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

The use of Methylphenidate LA Biotech 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 may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders

See section 4.3 for cerebrovascular conditions in which Methylphenidate LA Biotech treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with Methylphenidate LA Biotech.

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

Treatment with Methylphenidate LA Biotech 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, Methylphenidate LA Biotech 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 Methylphenidate LA Biotech 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 Methylphenidate LA Biotech at usual doses (see section 4.8). If manic or psychotic symptoms occur, consideration should be given to a possible causal role for Methylphenidate LA Biotech, and Methylphenidate LA Biotech 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 Methylphenidate LA Biotech 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 Methylphenidate LA Biotech treatment. Treatment of

an underlying psychiatric condition may be necessary, and consideration should be given to a possible discontinuation of Methylphenidate LA Biotech.

Tics

Methylphenidate as contained in Methylphenidate LA Biotech 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 Methylphenidate LA Biotech for ADHD treatment. Patients should be regularly monitored for the emergence or worsening of tics during treatment with Methylphenidate LA Biotech. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension

Methylphenidate as contained in Methylphenidate LA Biotech is associated with the worsening of pre-existing anxiety, agitation or tension. Patients should be regularly monitored for the emergence or worsening of tics during treatment with Methylphenidate LA Biotech. Monitoring should be 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 stimulants to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with Methylphenidate LA Biotech, 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.

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

Abuse, misuse and diversion

Patients should be carefully monitored for the risk of diversion, misuse and abuse of Methylphenidate LA Biotech.

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

Chronic abuse of Methylphenidate LA Biotech can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, Methylphenidate LA Biotech or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal

Careful supervision is required during Methylphenidate LA Biotech 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 Methylphenidate LA Biotech from abusive use since severe depression may occur.

Fatigue

Methylphenidate LA Biotech 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 Methylphenidate LA Biotech in patients with renal or hepatic insufficiency.

Haematological effects

The long-term safety of treatment with Methylphenidate LA Biotech 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.

Increased intraocular pressure and glaucoma

There have been reports of increased intraocular pressure (IOP) and glaucoma (including open angle glaucoma and angle closure glaucoma) associated with methylphenidate treatment as contained in Methylphenidate LA Biotech (see section 4.8). Patients should be advised to contact their doctor in case of experiencing symptoms suggestive of increased IOP and glaucoma. An ophthalmologist should be consulted and discontinuation of Methylphenidate LA Biotech be considered if IOP increases (see section 4.3).

Ophthalmologic monitoring of patients with a history of increased IOP is recommended.

Excipient: sucrose

Methylphenidate LA Biotech contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose isomaltose insufficiency should not take Methylphenidate LA Biotech.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interaction

It is not known how Methylphenidate LA Biotech may affect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended at combining Methylphenidate LA Biotech with other medicines, 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 Methylphenidate LA Biotech, it may be necessary to adjust the dosage of these medicines already being taken and establish the plasma concentrations of other medicines (or for warfarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive medicines

Methylphenidate LA Biotech may decrease the effectiveness of active substances used to treat hypertension.

Use with medicines that elevate blood pressure

Caution is advised in patients being treated with Methylphenidate LA Biotech with any other active substance that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

Because of possible hypertensive crisis, Methylphenidate LA Biotech is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive active substances, including Methylphenidate LA Biotech. 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 Methylphenidate LA Biotech with dopaminergic active substances, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, Methylphenidate LA Biotech 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

Methylphenidate LA Biotech 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

Methylphenidate LA Biotech is contraindicated in pregnancy (see section 4.3).

Breastfeeding

Methylphenidate has been found in the breast milk of a woman treated with methylphenidate. Methylphenidate LA Biotech should not be used during breastfeeding (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

Methylphenidate LA Biotech can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision.

Patients on Methylphenidate LA Biotech experiencing these adverse effects should not drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System Organ Class	**Frequency**		
	Less frequent	**Frequent**	**Not known**
Infections and infestations	nasopharyngitis	gastroenteritis	
Blood and lymphatic system disorders		anaemia[#], leukopenia[#], thrombocytopenia, thrombocytopenic purpura	pancytopenia
Immune system disorders		Hypersensitivity reactions such as	

		angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rashes, and eruptions	
Metabolism and nutrition disorders*	anorexia, decreased appetite, reduced weight and height gain during prolonged use in children*, weight decrease in adults		
Psychiatric disorders*	insomnia, nervousness, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal	psychotic disorders*, auditory, visual and tactile hallucination* anger, suicidal ideation*, mood swings[#], tearfulness, tics*, worsening of pre-existing tics of Tourette's syndrome*,	delusions*, thought disturbances*, confusional state, dependence, cases of abuse and dependence have been described, more often with immediate release formulations, logorrhoea

	behaviour, bruxism[∞], panic attack***, stress***, restlessness[#], sleep disorder[#], libido decreased	hypervigilance, tension***, mania*, libido disorder, disorientation, suicidal attempt (incl. completed suicide) *, transient depressed mood*, abnormal thinking, apathy[#], obsessive-compulsive disorder (including trichotillomania and dermatillomania)	
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	Cerebrovascular disorders* (incl. vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion*, migraine[#], paraesthesia[$], aphasia[$#], dysphemia

		were also receiving other medicines, so the role of methylphenidate is unclear)	
Eye disorders		diplopia, blurred vision[#], difficulties in visual accommodation, mydriasis, visual disturbance, dry eye[$]	ocular hypertension, increased intraocular pressure, glaucoma
Cardiac disorders*	palpitations, dysrhythmia, tachycardia	chest pain, angina pectoris, cardiac arrest, myocardial infarction	supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles, cardiac discomfort[$]
Vascular disorders*	Hypertension	cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon	hot flush[$], flushing[$]
Respiratory, thoracic and mediastinal disorders	cough, pharyngolaryngeal pain, dyspnoea		oropharyngeal pain[$], epistaxis[$]
Gastrointestinal disorders	abdominal pain, diarrhoea, nausea, stomach	constipation	retching[$]

	discomfort, vomiting - these usually occur at the beginning of treatment and may be alleviated by concomitant food intake, dry mouth dyspepsia,*** toothache***		
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$^{\infty}$
Renal and urinary		haematuria	incontinence

disorders			
Reproductive system and breast disorders		gynaecomastia, menstruation disorder[$], impairment of libido[$]	erectile dysfunction, priapism, increased erection and prolonged erection, breast pain[$]
General disorders and administration site conditions	pyrexia, growth retardation during prolonged use in children, feeling jittery, fatigue, thirst***,	sudden cardiac death*	hyperpyrexia, disturbance in attention[$], influenza like illness[$], asthenia[$]
Investigations	changes in blood pressure and heart rate (usually, an increase)*, weight decreased	cardiac murmur, hepatic enzyme increased, blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal	blood thyroid stimulating hormone 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 adult clinical trials and not on data from trials in children and adolescents; may also be 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 drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from formulations with extended durations of action.

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 dysrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment

There is no specific antidote to Methylphenidate LA Biotech 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.

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 LA 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 LA 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.

Sprinkle administration

The C_{max}, t_{max} and AUC of the sprinkled contents of the Methylphenidate LA Biotech capsule are similar (bioequivalent) to the intact capsule. Methylphenidate LA Biotech 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 %).

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 %).

Specific 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Ammonio methacrylate copolymer (type B)

Methacrylic acid - methyl methacrylate copolymer (1:1)

Povidone 30

Sugar spheres (containing sucrose and maize starch)

Talc

Triethyl citrate

Capsule shell

Gelatin

Titanium dioxide (E171)

Additionally in Methylphenidate 10 LA Biotech, Methylphenidate 30 LA Biotech, Methylphenidate 40 LA

Biotech and Methylphenidate 60 LA Biotech: Iron oxide yellow (E172).

Printing ink

Potassium hydroxide

Propylene glycol

Red iron oxide (E 172)

Shellac glaze

Strong ammonia solution

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years if stored below 30 °C.

If the capsules are removed from the blister, it should be used within 4 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Child resistant unit-dose blisters (white opaque Aclar/PVC//Al/PET) boxed in cardboard cartons.

10 mg: 28, 30, 50, 56, 60, 100 capsules.

20 mg: 28, 30, 50, 56, 60, 84, 100 capsules.

30 mg: 28, 30, 50, 56, 60, 100 capsules.

40 mg: 28, 30, 50, 56, 60, 100 capsules.

60 mg: 28, 30, 50, 56, 60, 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

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Midrand

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8. REGISTRATION NUMBER(S)

Methylphenidate 10 LA Biotech: 57/1.2/0758

Methylphenidate 20 LA Biotech: 57/1.2/0759

Methylphenidate 30 LA Biotech: 57/1.2/0760

Methylphenidate 40 LA Biotech: 57/1.2/0761

Methylphenidate 60 LA Biotech: 57/1.2/0762

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 October 2025

10. DATE OF REVISION OF THE TEXT

16 July 2026