

PROFESSIONAL INFORMATION

METHYLPHENIDATE BIOTECH 10

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

METHYLPHENIDATE BIOTECH 10 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg methylphenidate hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White, round, flat scored tablet marked with "RU 10" on one side. Diameter 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention deficit hyperactivity disorder (ADHD) in children aged 6 years or older.

Narcolepsy in adults.

4.2 Posology and method of administration

Posology

The dosage of METHYLPHENIDATE BIOTECH 10 should be individualised according to the patient's clinical needs and responses.

METHYLPHENIDATE BIOTECH 10 should be started at a low dose, with increments at weekly intervals.

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

If improvement is not observed after appropriate dosage adjustment over a one-month period, METHYLPHENIDATE BIOTECH 10 should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, METHYLPHENIDATE BIOTECH 10 should be discontinued.

Pre-treatment screening

Before initiating METHYLPHENIDATE BIOTECH 10 treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular dysrhythmia and psychiatric disorders (see sections 4.3 and 4.4).

NARCOLEPSY:

The average dosage is 20 to 30 mg daily, given in 2 to 3 divided doses. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if METHYLPHENIDATE BIOTECH 10 is taken late in the day should take the last dose before 6 p.m. (18:00).

A total daily dose of 60 mg should not be exceeded.

Periodic assessment of the treatment in ADHD

Medicine treatment should not and need not be indefinite.

METHYLPHENIDATE BIOTECH 10 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, METHYLPHENIDATE BIOTECH 10 can usually be discontinued after puberty.

ADHD:

Children and adolescents (6 years and older):

Start with 5 mg once or twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. The total daily dose should be administered in divided doses.

Daily dosage above 60 mg is not recommended.

Special populations

Elderly

Safety and efficacy have not been established in patients over 60 years of age.

Hepatic impairment

METHYLPHENIDATE BIOTECH 10 has not been studied in patients with hepatic impairment.

Caution should be exercised in these patients.

Renal impairment

METHYLPHENIDATE BIOTECH 10 has not been studied in patients with renal impairment.

Caution should be exercised in these patients.

Paediatric population

Children under 6 years of age

METHYLPHENIDATE BIOTECH 10 is not indicated in children less than six years of age.

Method of administration

METHYLPHENIDATE BIOTECH 10 is for oral administration and can be taken with or without food.

4.3 Contraindications

- Known hypersensitivity to methylphenidate or to any of the excipients of METHYLPHENIDATE BIOTECH 10 (see section 6.1).
- Anxiety, tension, agitation, a family history or diagnosis of Tourette's syndrome, hyperthyroidism or thyrotoxicosis, glaucoma, phaeochromocytoma.
- 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).
- 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 medicine (see section 4.4).
- 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).
- Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders.

4.4 Special warnings and precautions for use

General

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use METHYLPHENIDATE BIOTECH 10 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, and not simply on the presence of one or more abnormal behavioural characteristics.

METHYLPHENIDATE BIOTECH 10 should not be used for the treatment of attention deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

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

The safety and efficacy of long-term use of methylphenidate, as contained in METHYLPHENIDATE BIOTECH 10, have not been systematically evaluated in controlled trials. METHYLPHENIDATE BIOTECH 10 treatment should not and need not be indefinite.

Methylphenidate treatment is usually discontinued after puberty (see section 4.2). Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth, appetite, development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The medical practitioner who elects to use methylphenidate as contained in METHYLPHENIDATE BIOTECH 10 for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the medicine for the individual patient with trial periods off the medicine to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

Use in adults with ADHD

METHYLPHENIDATE BIOTECH 10 is not indicated for use in adults with ADHD. Safety and efficacy have not yet been established in this age group.

Use in the elderly

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

Use in children under 6 years of age

METHYLPHENIDATE BIOTECH 10 is not indicated in children less than six years of age.

Cardiovascular conditions

METHYLPHENIDATE BIOTECH 10 is contraindicated in patients with hypertension.

METHYLPHENIDATE BIOTECH 10 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).

Blood pressure should be monitored at appropriate intervals in all patients taking METHYLPHENIDATE BIOTECH 10. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during METHYLPHENIDATE BIOTECH 10 treatment should undergo a prompt cardiac evaluation.

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 structural cardiac abnormalities or other serious heart problems.

Although some serious heart problems alone may carry an increased risk of sudden death, METHYLPHENIDATE BIOTECH 10 is 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. Before initiating METHYLPHENIDATE BIOTECH

10 treatment, patients 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.

Misuse and cardiovascular events

Misuse of stimulants of the central nervous system, such as METHYLPHENIDATE BIOTECH 10, may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders

Patients with pre-existing central nervous system (CNS) abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with METHYLPHENIDATE BIOTECH 10.

Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with METHYLPHENIDATE BIOTECH 10.

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 BIOTECH 10 and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischaemia during METHYLPHENIDATE BIOTECH 10 therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with METHYLPHENIDATE BIOTECH 10 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 METHYLPHENIDATE BIOTECH 10. Prior to initiating treatment with METHYLPHENIDATE BIOTECH 10, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section 4.2). Treatment of ADHD with METHYLPHENIDATE BIOTECH 10 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 disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

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

Exacerbation of pre-existing psychotic or manic symptoms

In psychotic patients, administration of METHYLPHENIDATE BIOTECH 10 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 BIOTECH 10 at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants.

Patients treated with METHYLPHENIDATE BIOTECH 10 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 or every visit. Medical practitioners should evaluate the need for adjustment of the treatment regimen in patients experiencing 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 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 BIOTECH 10 treatment. Treatment of an underlying psychiatric condition may be necessary, and consideration should be given to a possible discontinuation of METHYLPHENIDATE BIOTECH 10.

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of METHYLPHENIDATE BIOTECH 10. Patients should be regularly monitored for the emergence or worsening of tics during treatment with METHYLPHENIDATE BIOTECH 10.

Anxiety, agitation or tension

METHYLPHENIDATE BIOTECH 10 is associated with the worsening of pre-existing anxiety, agitation or tension. METHYLPHENIDATE BIOTECH 10 is contraindicated in patients suffering from these conditions (see section 4.3).

Forms of bipolar disorder

Particular care should be taken in using METHYLPHENIDATE BIOTECH 10 to treat ADHD in patients with comorbid 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 BIOTECH 10, 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.**

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 METHYLPHENIDATE BIOTECH 10 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 METHYLPHENIDATE BIOTECH 10 and serotonergic medicines can be immediately discontinued, and appropriate treatment instituted (see section 4.5).

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.

Growth retardation

Moderately reduced body mass gain and growth retardation have been reported with long-term use of methylphenidate in children.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart.

Patients who are not growing or gaining height or body mass as expected may need to have their METHYLPHENIDATE BIOTECH 10 treatment interrupted and adjusted.

Seizures

METHYLPHENIDATE BIOTECH 10 should be used with caution in patients with epilepsy.

Methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, METHYLPHENIDATE BIOTECH 10 should be discontinued.

Abuse, misuse and dependence

Patients should be carefully monitored for the risk of diversion, misuse and abuse of METHYLPHENIDATE BIOTECH 10.

METHYLPHENIDATE BIOTECH 10 should be used with caution in patients with known medicine or alcohol dependency, because of a potential for abuse, misuse or diversion.

Chronic abuse of METHYLPHENIDATE BIOTECH 10 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 comorbid oppositional-defiant or conduct disorder and bipolar disorder), and 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 medicine or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, METHYLPHENIDATE BIOTECH 10 may not be suitable.

Withdrawal

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

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue

METHYLPHENIDATE BIOTECH 10 should not be used for the prevention or treatment of normal fatigued states.

Renal or hepatic insufficiency

There is no experience with the use of METHYLPHENIDATE BIOTECH 10 in patients with renal or hepatic insufficiency.

Haematological effects

The long-term safety of treatment with methylphenidate, as in METHYLPHENIDATE BIOTECH 10, is 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 leucopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

4.5 Interaction with other medicines and other forms of interaction

It is not known how methylphenidate, as contained in METHYLPHENIDATE BIOTECH 10, may affect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended at combining METHYLPHENIDATE BIOTECH 10 with other medicines, especially those with a narrow therapeutic window.

Pharmacokinetic interactions

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, as contained in METHYLPHENIDATE BIOTECH 10, may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclic and selective serotonin reuptake inhibitors).

When starting and stopping treatment with METHYLPHENIDATE BIOTECH 10, it may be necessary to adjust the dosage of these medicines that are already being taken and establish plasma concentrations (or for coumarin, coagulation times).

METHYLPHENIDATE BIOTECH 10 coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Pharmacodynamic interactions

Anti-hypertensive medicines

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

Use with medicines that elevate blood pressure

Caution is advised in patients being treated with METHYLPHENIDATE BIOTECH 10 with other

medicines that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

Because of possible hypertensive crisis, METHYLPHENIDATE BIOTECH 10 is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive medicines, including METHYLPHENIDATE BIOTECH 10. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with anaesthetics

There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, treatment with METHYLPHENIDATE BIOTECH 10 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.

Use with dopaminergic medicines

Caution is recommended when administering METHYLPHENIDATE BIOTECH 10 with dopaminergic medicines, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, METHYLPHENIDATE BIOTECH 10 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 serotonergic medicines

The concomitant use of METHYLPHENIDATE BIOTECH 10 and serotonergic medicines 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.

Medicine/Laboratory test

METHYLPHENIDATE BIOTECH 10 may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

4.6 Fertility, pregnancy and lactation

Pregnancy

METHYLPHENIDATE BIOTECH 10 is contraindicated during pregnancy (see section 4.3).

There is a limited amount of data from the use of methylphenidate, as contained in METHYLPHENIDATE BIOTECH 10, in pregnant women.

Breastfeeding

METHYLPHENIDATE BIOTECH 10 is contraindicated during lactation as safety has not been demonstrated (see section 4.3).

Mothers taking METHYLPHENIDATE BIOTECH 10 should not breastfeed their infants.

Methylphenidate, as contained in METHYLPHENIDATE BIOTECH 10, has been found in breast milk of women treated with methylphenidate.

Fertility

No human data exists regarding the effect of methylphenidate on fertility. No clinically relevant effects on fertility have been observed in animal studies.

4.7 Effects on ability to drive and use machines

METHYLPHENIDATE BIOTECH 10 may cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision (see section 4.8). It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving a vehicle or operating machinery.

4.8 Undesirable effects

Infections and infestations

Frequent: nasopharyngitis

Less frequent: gastroenteritis²

Blood and lymphatic disorders

Less frequent: anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura

Frequency unknown: pancytopenia

Immune system disorders

Less frequent: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritis, rashes and eruptions

Metabolism and nutritional disorders*

Frequent: anorexia, decreased appetite, moderately reduced body mass and height gain during prolonged use in children

Psychiatric disorders*

Frequent: insomnia, nervousness, affect lability, aggression*, agitation*, anxiety*,

depression*, irritability, abnormal behaviour, restlessness¹, sleep disorder¹,
impaired libido², panic attacks², stress², bruxism³

Less frequent: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger,
suicidal ideation*, mood altered, mood swings, tearfulness, tics*, worsening
of pre-existing tics or Tourette's syndrome*, hypervigilance, mania*,
disorientation, libido disorder, suicidal attempt (including completed
suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive
behaviours, over-focussing

Frequency unknown: delusions*, thought disturbances*, confusional state, dependence,
logorrhoea.

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

Nervous system disorders

Frequent: headache, dizziness, dyskinesia, psychomotorhyperactivity, somnolence,
tremors¹

Less frequent: sedation, convulsions, choreo-athetoid movements, reversible ischaemic
neurological deficit, neuroleptic malignant syndrome (NMS) (reports were
poorly documented and, in most cases, patients were also receiving other
medicines, so the role of methylphenidate is unclear)

Frequency unknown: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages,
cerebrovascular incidents, cerebral arteritis, cerebral occlusion), grand mal
convulsions*, migraine, dysphemia

Eye disorders

Less frequent: diplopia, blurred vision, difficulties in visual accommodation, mydriasis,
visual disturbance

Cardiac disorders*

Frequent: dysrhythmia, tachycardia, palpitations

Less frequent: chest pain, angina pectoris, cardiac arrest, myocardial infarction, sudden cardiac death*

Frequency unknown: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*

Frequent: hypertension, peripheral coldness¹

Less frequent: cerebral arteritis and/or occlusion, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Frequent: cough, pharyngolaryngeal pain, dyspnoea¹

Frequency unknown: epistaxis

Gastrointestinal disorders

Frequent: abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting (these usually occur at the beginning of treatment and may be alleviated by concomitant food intake), dry mouth

Less frequent: constipation

Hepatobiliary disorders

Less frequent: hepatic enzyme elevations, abnormal liver functions, including hepatic coma

Skin and subcutaneous tissue disorders

Frequent: alopecia, pruritis, rash, urticaria, hyperhidrosis¹

Less frequent: angioneurotic oedema, bullous conditions, exfoliate conditions, hyperhidrosis, macular rash, erythema, erythema multiforme, exfoliate

dermatitis, fixed medicine eruption

Musculoskeletal, connective tissue and bone disorders

Frequent: arthralgia

Less frequent: myalgia, muscle twitching, muscle cramps, muscle tension²

Frequency unknown: trismus³

Renal and urinary disorders

Less frequent: haematuria

Frequency unknown: incontinence

Reproductive system and breast disorders

Less frequent: gynaecomastia

Frequency unknown: erectile dysfunction, priapism, increased erection and prolonged erection

General disorders and administration site conditions

Frequent: pyrexia, growth retardation during prolonged use in children*, fatigue, thirst

Frequency unknown: chest discomfort, hyperpyrexia

Investigations

Frequent: changes in blood pressure and heart rate (usually an increase)*, decreased body mass*

Less frequent: cardiac murmur*, increased hepatic enzyme, increased blood alkaline phosphatase, increased blood bilirubin, decreased platelet count, abnormal white blood count.

* See section 4.4 “Special warnings and precautions for use”.

¹ Adverse effects from clinical studies in adult patients that reported a higher frequency than in

children and adolescents.

² Adverse effects from clinical studies in adult patients that did not report on children and adolescents.

³ 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 METHYLPHENIDATE BIOTECH 10 is important. It allows continued monitoring of the benefit/risk balance of METHYLPHENIDATE BIOTECH 10. Health care providers are asked to report any suspected adverse reactions via the via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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, dryness of mucous membranes and rhabdomyolysis.

Treatment

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 medical practitioner should consult a certified poison centre or current toxicological publication.

The patient must be protected against self-injury and against external stimuli that would aggravate

over-stimulation already present. If the patient is conscious, administration of activated charcoal and a laxative is recommended. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given.

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 overdose of methylphenidate has not been established.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 1.2 Psychoanaleptics (antidepressants)

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics, ATC code: NO6B AO4.

Mode 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 an 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.

Methylphenidate is a racemic mixture containing d- and l-enantiomers, where the d-enantiomer is considered as the pharmacologically active enantiomer.

5.2 Pharmacokinetic properties

Absorption

The active substance methylphenidate hydrochloride is rapidly and almost completely absorbed from the tablets. Owing to extensive first-pass metabolism the absolute bioavailability was 22 ± 8 % for the d-enantiomer and 5 ± 3 % for the l-enantiomer. Ingestion together with food increased

both the peak plasma concentration (C_{max}) by 23 % and the area under the concentration-time curve (AUC) by 15 %, but had no relevant effect on the rate of absorption of methylphenidate. Peak plasma concentrations of approximately 40 nmol/L (11 ng/mL) are attained, on average, 1 – 2 hours after administration of 0,30 mg/kg. The peak plasma concentrations, however, show considerable intersubject variability. The AUC and the C_{max} are proportional to 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 rate (10 – 33 %). The volume of distribution was $2,65 \pm 1,11$ L/kg for d-MPH and $1,80 \pm 0,91$ L/kg for l-MPH.

Biotransformation

Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Peak plasma concentrations of α -phenyl-2-piperidyl acetic acid (ritalinic acid) (PPAA) are attained approximately 2 hours after administration of methylphenidate and are 30 – 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. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

Elimination

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The systemic clearance is $0,40 \pm 0,12$ L/h/kg for d-MPH and $0,73 \pm 0,28$ L/h/kg for l-MPH. Within 48 – 96 hours 78 – 97 % of the dose administered is excreted in the urine and 1 – 3 % in the faeces in the form of metabolites. Unchanged methylphenidate appears in the urine only in small quantities (< 1 %). The bulk of the dose is excreted in the urine as PPAA (60 – 86 %).

Special populations

Gender

There is no relevant difference in pharmacokinetic parameters between male and female healthy volunteers or patients.

Ethnic background

The values for dose-adapted AUC for methylphenidate are the same for all ethnic groups. There may be insufficient data to prove ethnic variations with regard to pharmacokinetic properties.

Age

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

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.

Hepatic impairment

There is no experience of treatment of patients with hepatic impairment.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose.

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

- Store at or below 25 °C. Protect from moisture.
- Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

PVC/aluminium blister strip, containing ten tablets.

Three blister strips are packed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

Tel. no.: 011 848 3050

8. REGISTRATION NUMBER

Methylphenidate Biotech 10: 49/1.2/1000

9. DATE OF FIRST AUTHORISATION

04 August 2020.

10. DATE OF REVISION OF THE TEXT

06 March 2025.