PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Methylphenidate HCl-Douglas 10 mg. Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methylphenidate hydrochloride 10 mg.

Contains sugar: Lactose 53,00 mg/tablet

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White or off-white, circular, flat bevel-edged tablets, engraved “M” break line “P” on one face and “10” on the other face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

METHYLPHENIDATE HCL-DOUGLAS 10 mg tablets are indicated for:

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

The diagnosis should be made in accordance with the guidelines from International Classification of Diseases (ICD) or DSM criteria
and should be based on a complete history and evaluation of the patient.

4.2 Posology and method of administration

Posology

METHYLPHENIDATE HCL-DOUGLAS 10 mg is part of an extended treatment program for attention deficit hyperactivity disorder, which includes psychological, educational and social remedial measures.

The dosage should be individually adapted to the patient's requirements and to the indication, as well as their clinical needs and responses.

METHYLPHENIDATE HCL-DOUGLAS 10 mg should be started at a low dose, with increments at weekly intervals.

If an improvement is not observed after appropriate dosage adjustment over a period of one-month, METHYLPHENIDATE HCL-DOUGLAS 10 mg should be discontinued.

METHYLPHENIDATE HCL-DOUGLAS 10 mg should be discontinued
if paradoxical aggravation of symptoms or other adverse effects occur.

Pre-treatment screening:

Prior to initiating treatment with **METHYLPHENIDATE HCL-DOUGLAS**
10 mg, patients should be assessed for their cardiovascular status, including their blood pressure and heart rate. A comprehensive history should document concomitant medicines, pre-existing and currently present co-morbid medical and psychiatric disorders or symptoms, any family history of sudden cardiac/unexplained death and recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4).

Ongoing monitoring:

Growth, cardiovascular and psychiatric status should be continuously monitored in patients (see section 4.4).

- Pulse and blood pressure should be recorded at each adjustment of dose and thereafter at least every 6 months;
- Appetite, height and weight should be recorded at least 6-monthly with the maintenance of a growth chart;
- Development of new psychiatric disorders, or worsening of pre-existing psychiatric disorders, should be monitored with each dosage adjustment, and thereafter at least every 6 months and at every visit.

Patients should be continuously monitored for the risk of abuse, misuse or diversion of **METHYLPHENIDATE HCL-DOUGLAS 10 mg.**

NARCOLEPSY:

Adults

In the treatment of narcolepsy, the usual dosage is 20 mg to 30 mg daily, taken preferably 30 to 45 minutes before a meal. The effective dose may range from 10 mg to 60 mg in divided doses. To minimise the risk of insomnia, the last dose should be taken not later than 18h00.

The recommended dosage is 20 mg one to three times daily at eight-hour intervals.

ADHD:

Children and adolescents 6 years and older

The starting dose should be 5 mg before breakfast and 5 mg before lunch, the daily dosage subsequently being raised by 5 mg to 10 mg each week to a level not higher than 60 mg per day. The total daily dosage should be administered in divided doses.

The dosage can also be expressed in terms of body weight; usual doses are 0,25 mg per kg daily, doubled each week to 2 mg per kg.

Methylphenidate's administration should coincide with periods of greatest academic, behavioural, and social difficulties for the patient.

In some children sleeplessness occurs because the effect of the medicine deteriorates in the evening. Such children may then rebound to their usual level of activity or distraction. This problem may be dealt with by administering an additional short-acting dose of the stimulant at about 20h00. A trial dose at bedtime is necessary to clarify the issue.

METHYLPHENIDATE HCl-DOUGLAS 10 mg should be periodically discontinued to assess the child's condition. It is recommended that methylphenidate, as contained in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, is de-challenged at least once a year (preferably during school holidays) to perform this assessment.

Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

Treatment with METHYLPHENIDATE HCl-DOUGLAS 10 mg should not and need not be indefinite and usually may be discontinued during or after puberty.

Special populations

Elderly

METHYLPHENIDATE HCl-DOUGLAS 10 mg should not be used in the elderly, safety and efficacy has not been established in this age group.

Children under 6 years of age

METHYLPHENIDATE HCl-DOUGLAS 10 mg should not be used in children under the age of 6 years. Safety and efficacy in this group has not been established.

Hepatic impairment

Methylphenidate, as in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, has not been studied in patients with hepatic impairment. Caution should be exercised in these patients.

Renal impairment

Methylphenidate, as in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, has not been studied in patients with renal impairment. Caution should be exercised in these patients.

Method of administration

METHYLPHENIDATE HCl-DOUGLAS 10 mg tablets are to be taken orally.

4.3 Contraindications

- Known hypersensitivity to methylphenidate or any of the excipients of **METHYLPHENIDATE HCl-DOUGLAS 10 mg**.
- Anxiety, tension, agitation
- Diagnosis of, or a family history of Tourette's syndrome.
- Pre-existing cardiovascular disorders including hypertension, angina pectoris, heart failure, arterial occlusive disease, haemodynamically significant congenital heart disease, myocardial infarction, cardiomyopathies, potential life-threatening dysrhythmias, channelopathies (disorders caused by the dysfunction of ion channels) and QT prolongation either congenital, familial or caused by medicines (see section 4.4).
- Glaucoma.
- Hyperthyroidism.
- Pheochromocytoma.
- Methylphenidate should not be given to patients being treated with mono-amine oxidase inhibitors or within 14 days of stopping the treatment thereof, due to the risk of hypertensive crisis (see section 4.5).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

METHYLPHENIDATE HCl-DOUGLAS 10 mg should not be used as a stimulant for the prevention or treatment of normal fatigue states.

Paediatric patients under 6 years of age

METHYLPHENIDATE HCl-DOUGLAS 10 mg treatment is not indicated in all cases of ADHD and should be considered based on a very thorough assessment of the severity of symptoms, and, in paediatric patients, the appropriateness to the age of the child and not simply on the presence of one or more abnormal behavioural characteristic.

METHYLPHENIDATE HCL-DOUGLAS 10 mg is usually not indicated when the symptoms are associated with acute stress reactions.

Cardiovascular:

Pre-existing structural cardiac abnormalities or other serious cardiac problems:

Sudden death has been reported in association with the use of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, at normal doses in patients with pre-existing structural cardiac abnormalities or other serious heart problems. A causal relationship with methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg,** has not been established as some of these conditions alone may carry an increased risk of sudden death.

Before initiating treatment with **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, 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).

METHYLPHENIDATE HCL-DOUGLAS 10 mg 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.

Misuse and Cardiovascular Events:

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

Cardiovascular conditions:

METHYLPHENIDATE HCL-DOUGLAS 10 mg is contraindicated in patients with hypertension. Methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, increases systolic and diastolic blood pressure and heart rate. Caution is indicated in treating patients whose underlying medical conditions might be compromised by an increase 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 HCL-DOUGLAS 10 mg**.

Patients who develop symptoms suggestive of cardiac disease during treatment with **METHYLPHENIDATE HCL-DOUGLAS 10 mg** should undergo a prompt specialist cardiac evaluation.

Cerebrovascular disorders:

Patients with pre-existing central nervous system abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with **METHYLPHENIDATE HCL-DOUGLAS 10 mg**.

Patients with additional risk factors (such as concomitant medications that elevate blood pressure, history of cardiovascular disease) should be assessed regularly for neurological signs and symptoms after initiating **METHYLPHENIDATE HCL-DOUGLAS 10 mg** treatment (see above, paragraph on *Cardiovascular Conditions* and section 4.5).

Psychiatric:

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when **METHYLPHENIDATE HCL-DOUGLAS 10 mg** is prescribed. Prior to initiating **METHYLPHENIDATE HCL-DOUGLAS 10 mg** treatment, 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 HCL-DOUGLAS 10 mg** should not be introduced in patients with acute mania, acute psychosis, 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, **METHYLPHENIDATE HCL-DOUGLAS 10 mg** should not be given to patients unless the benefits outweigh the potential risks to the patient.

The administration of methylphenidate may exacerbate the symptoms of behavioural disturbance and thought disorder in psychotic patients.

***Psychotic symptoms*:** Treatment emergent psychotic symptoms, including visual, auditory and tactile hallucinations and delusions or mania have been reported in patients administered recommended therapeutic doses of **METHYLPHENIDATE HCL-DOUGLAS 10 mg** (see section 4.8). Medical practitioners should consider treatment discontinuation if manic or psychotic symptoms occur.

***Aggressive or hostile behaviour*:** The emergence of aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during treatment with methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**. However, patients with ADHD may experience aggression as part of their medical condition. Therefore, a causal association with treatment may be difficult to assess.

Patients should be closely monitored for the emergence or worsening of aggressive behaviour or hostility.

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 or 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, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, 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, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, for ADHD treatment.

METHYLPHENIDATE HCL-DOUGLAS 10 mg 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 HCL-DOUGLAS 10 mg**.

***Serotonin syndrome*:** Serotonin syndrome has been reported following co-administration of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of **METHYLPHENIDATE HCL-DOUGLAS 10 mg** 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, diarrhea). Prompt recognition of these symptoms is important so that treatment with **METHYLPHENIDATE HCL-DOUGLAS 10 mg** and serotonergic medicines can be immediately discontinued and appropriate treatment instituted (see section 4.5).

Anxiety, agitation or tension: Methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, is associated with the exacerbation of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede the use of **METHYLPHENIDATE HCL-DOUGLAS 10 mg** and patients should be monitored regularly for the emergence or worsening of these symptoms.

Forms of bipolar disorder: **METHYLPHENIDATE HCL-DOUGLAS 10 mg** should be used with care to treat ADHD in patients with co morbid bipolar disorder (including untreated type 1 bipolar disorder) due to concern for possible precipitation of a mixed/manic episode in such patients. Patients with co morbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder, including a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close monitoring is essential in these patients (see section 4.2).

Priapism**:** Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, in both adult and paediatric patients. In general, priapism developed after some time on the medicine, often subsequent to an increased dose. Priapism has also been reported during a period of medicine withdrawal (drug 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 methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg** (see section 4.8). Growth, weight and appetite should be monitored during treatment with **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, and patients who are not growing or 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 methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, 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 such as leucopenia, thrombocytopenia, anaemia or other alterations, appropriate medical intervention should be considered (see section 4.8).

Seizures:

Clinical experience has shown that methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, can cause an increase in seizure frequency**.** If seizure frequency increases, or new-onset seizures occur, methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, should be discontinued.

Renal or hepatic insufficiency:

There is no experience with the use of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, in patients with renal or hepatic insufficiency.

Drug abuse and dependence: Chronic abuse of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially with parenteral abuse. Methylphenidate may be abused by predisposed patients, e.g.

in emotionally unstable individuals or those with a history of drug dependence or alcoholism. It should therefore be used only under very strict medical supervision as they may increase the dosage on their own initiative.

Withdrawal: During withdrawal of **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, mental depression as well as the effects of chronic over-activity can be exposed. Careful supervision is thus required during withdrawal of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, as severe depression may occur. Long-term follow-up may be needed for some patients.

Drug screening: **METHYLPHENIDATE HCL-DOUGLAS 10 mg** contains methylphenidate which may induce a false positive laboratory test for amphetamines.

Excipients with known effects: **METHYLPHENIDATE HCL-DOUGLAS 10 mg** contains 53 mg lactose per tablet. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **METHYLPHENIDATE HCL-DOUGLAS 10 mg.** Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

METHYLPHENIDATE HCL-DOUGLAS 10 mg 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 the pharmacokinetics of **METHYLPHENIDATE HCL-DOUGLAS 10 mg**.

Conversely, the d- and l- enantiomers of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Co-administration of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports suggested a potential interaction of methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, with warfarin, some anticonvulsants (e.g. phenobarbital, phenytoin, primidone) and tricyclic antidepressants (e.g. imipramine, desipramine) although pharmacokinetic interactions were not confirmed when explored at higher sample sizes.

When starting and stopping treatment with **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, it may be necessary to adjust the dosage of these medicines.

Pharmacokinetic interactions:

Anti-hypertensive medicines

Methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, may decrease the antihypertensive effect of guanethidine and it should be used cautiously with pressor agents including beta blockers. **METHYLPHENIDATE HCL-DOUGLAS 10 mg** 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 HCL-DOUGLAS 10 mg** with other medicines that can also elevate blood pressure (see section 4.4, cardiovascular and cerebrovascular conditions).

METHYLPHENIDATE HCL-DOUGLAS 10 mg is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors, due to possible hypertensive crisis (see section 4.3).

Use with alcohol

Alcohol may exacerbate the CNS adverse reactions of psychoactive **[**~~drugs~~**]** medicines, including methylphenidate. It is advisable for patients to abstain from alcohol during treatment.

Use with anaesthetics

There is a risk of sudden increase in blood pressure and heart rate during surgery. If surgery is planned, **METHYLPHENIDATE HCL-DOUGLAS 10 mg** should not be taken on the day of surgery.

Use with dopaminergic medicines

As a dopamine reuptake inhibitor, **METHYLPHENIDATE HCL-DOUGLAS 10 mg** 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 **METHYLPHENIDATE HCL-DOUGLAS 10 mg** with antipsychotics is not recommended due to the counteracting mechanism of action.

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, dexmedetomidine or other centrally acting alpha-2 agonists, although no causality for the combination has been established.

Use with serotonergic medicines

The concomitant use of **METHYLPHENIDATE HCL-DOUGLAS 10 mg** and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome (see section 4.4). Methylphenidate, as contained in **METHYLPHENIDATE HCL-DOUGLAS 10 mg**, has been shown to increase extracellular norepinephrine serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Urinary excretion may be reduced by urinary alkalinisers, which may enhance or prolong the effect of methylphenidate; excretion may be increased by urinary acidifiers.

4.6 Fertility, pregnancy and lactation

Pregnancy

METHYLPHENIDATE HCl-DOUGLAS 10 mg is contraindicated and should not be used during pregnancy as safety has not been demonstrated**.**

Lactation

METHYLPHENIDATE HCl-DOUGLAS 10 mg is contraindicated and should not be used during lactation as safety has not been demonstrated.

Fertility

No human data on the effect of methylphenidate, as contained in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, on fertility are available. Methylphenidate did not impair fertility in male or female mice (see section 5.3)

4.7 Effects on ability to drive and use machines

METHYLPHENIDATE HCl-DOUGLAS 10 mg may cause dizziness, visual disturbances including difficulties with accommodation, diplopia and blurred vision, and drowsiness. It is therefore advisable to exercise caution when driving, operating machines or engaging in other potentially hazardous activities.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Common adverse reactions are nervousness, insomnia and a decreased appetite. Nervousness and insomnia usually occur at the beginning of the treatment and may be controlled by reducing the dose and omitting the medicine in the afternoon or evening. The decrease in appetite is usually a transient feature.

Abdominal pain, nausea and vomiting are common to very common. These usually occur at the beginning of treatment and may be alleviated by concomitant food intake.

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, as contained in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, played in these cases.

Tabulated summary of adverse drug reactions

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked according to frequency, with the most frequent adverse reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Frequency	Side effect
Infections and infestations	Frequent	Nasopharyngitis
Blood and lymphatic system disorders	Frequent	Risk of epistaxis*
	Less frequent	Leucopenia, thrombocytopenia, anaemia
	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 weight and height gain during prolonged use in children.
Psychiatric disorders	Frequent	Insomnia, nervousness, anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour, bruxism

	Less frequent	Psychotic disorders, auditory, visual and tactile hallucinations, anger, suicidal ideation, mood altered, mood swings, restlessness, tearfulness, tics, worsening of pre-existing tics or Tourette's syndrome, hypervigilance, sleep disorder, mania, disorientation, libido disorder, suicidal attempt (including completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focusing
	Frequency unknown	Delusions, thought disturbances, confusional state, dependence, logorrhea
Nervous system disorders	Frequent	Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence
	Less frequent	Sedation, tremor, convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS)
	Frequency unknown	Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, 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	Arrhythmia, tachycardia palpitations
	Less frequent	Chest pain, angina pectoris, cardiac arrest, myocardial infarction
	Frequency unknown	Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders	Frequent	Hypertension
	Less frequent	Peripheral coldness, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, pharyngo-laryngeal pain
	Less frequent	Dyspnoea
Gastro-intestinal disorders	Frequent	Abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting. 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
	Less frequent	Angioneurotic oedema, bullous conditions, exfoliative conditions, hyperhidrosis, macular rash, erythema, erythema multiforme, exfoliative dermatitis, fixed medicine eruption.
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia
	Less frequent	Myalgia, muscle twitching, muscle cramps
	Frequency unknown	Trismus
Renal and urinary disorders	Less frequent	Haematuria
	Frequency unknown	Incontinence
Reproductive system and breast disorders	Less frequent	Gynaecomastia
	Frequency unknown	Erectile dysfunction, priapism, erection increased and prolonged erection
	Frequent	Pyrexia, growth retardation during prolonged use in children

General disorders and administration site conditions	Less frequent	Chest pain, fatigue, sudden cardiac death
	Frequency unknown	Chest discomfort, hyperpyrexia
Investigations	Frequent	Blood pressure and heart rate changes (usually an increase), decreased weight
	Less frequent	Cardiac murmur, increased hepatic enzyme, blood alkaline, phosphatase and blood bilirubin increased, platelet count decreased, abnormal white blood count.

*****Adverse effect observed post marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in agitation, cardiac arrhythmias, confusion, delirium, panic states, dryness of mouth or mucous membranes, euphoria, fever, hallucinations, headache, hyperreflexia, increased blood pressure, chest pain, respiratory depression, increased sweating, flushing, muscle twitching, mydriasis, palpitations, seizures/convulsions (may be followed by coma), tachycardia, trembling or tremors, vomiting, circulatory collapse and coma, rhabdomyolysis.

Individual patient response may vary widely, and toxic manifestations may occur at relatively low doses.

Treatment

There is no specific antidote to methylphenidate, as contained in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, overdosage.

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events e.g. hypertensive crisis, cardiac dysrhythmias, convulsions.

Supportive measures include **[**~~with~~**]** the possible utilisation of the following:

- The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present.
- If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be emptied by emesis or gastric lavage.
- Before performing gastric lavage, control agitation and seizures if present and protect the airway.
- Other measures to detoxify the gut include administration of activated charcoal and a cathartic.
- For a severe overdose, a short-acting barbiturate should be administered using carefully titrated dosage before performing gastric lavage.
- Intensive care must be provided to maintain adequate circulatory and respiratory function.
- External cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdosage of methylphenidate, as contained in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Psychostimulants

ATC code: NO6B AO4

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

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.

The simultaneous ingestion of food increases both the peak plasma concentration (C_{max}) by 23 % and the area under the concentration-time curve (AUC) by 15 %, but has no influence on the amount absorbed.

The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, is proportional to the size of the dose administered.

Distribution:

In the blood, methylphenidate and its metabolites are distributed 57 % in plasma and 43 % in the erythrocytes. The plasma protein-binding of methylphenidate and its metabolites are low (10 to 33 %) with an apparent distribution volume calculated as 13,1 litre/kg. 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).

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. 78 to 97 % of the

administered dose is excreted in the urine and 1 to 3 % is excreted in the faeces in the form of metabolites within 48 to 96 hours. The bulk of the dose (60 to 86 %) is excreted in the urine as 2-phenyl-2-piperidyl acetic acid (PPAA) while less than 1 % of unchanged methylphenidate appears in the urine.

Biotransformation:

PPAA reaches peak plasma concentrations approximately 2 hours after administration of methylphenidate. The peak plasma concentrations are 30 to 50 times higher than those of the unchanged methylphenidate. The half-life of PPAA is approximately twice as long as that of methylphenidate, and the mean systemic clearance is 0,17 litres/h/kg.

Characteristics in patients:

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

Impaired renal function hardly decreases the renal excretion of the unchanged methylphenidate, however, renal excretion of PPAA is reduced.

5.3 Preclinical safety data

Carcinogenicity

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were only noted in male mice. The significance of this finding to humans is unknown. Methylphenidate, as in **METHYLPHENIDATE HCl-DOUGLAS 10 mg**, did not affect reproductive performance or fertility at low multiples of the clinical dosage.

Pregnancy-embryonal/foetal development

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

microcrystalline cellulose (Avicel PH102)

pregelatinised maize starch

stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep the blister in the outer carton until required for use.

Store at or below 30 °C.

Protect from light and moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister packs of 30 tablets, 10 tablets per blister, packed in an outer carton.

6.6 Special precautions for disposal and other handling

None

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

1685

8 REGISTRATION NUMBER

36/1.2/0234

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 March 2003

10 DATE OF REVISION OF THE TEXT

22 November 2022