DATA SHEET

METHYLPHENIDATE

Methylphenidate hydrochloride 10 mg tablets

Presentation

Methylphenidate in:
10 mg tablets are white or off-white, circular, flat, bevel-edged tablets, engraved “M” breakline “P” on one face and “10” on the other face.

Uses

Actions

Methylphenidate tablets are a central nervous system stimulant. Its mode of action in humans is not completely understood, but it is thought to exert its stimulant effect by activating the brainstem arousal system and cortex. The mechanism by which **Methylphenidate** tablets produces 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.

Pharmacokinetics

After oral administration, the active substance (methylphenidate hydrochloride) is rapidly and almost completely absorbed. Owing to extensive first-pass metabolism its systemic availability is only 30% (11-51%) of the dose. Ingestion with food accelerates absorption, but has no effect on the amount absorbed. Peak plasma concentrations of about 40 nmol/L (11 ng/ml) are reached on average 1-2 hours after administration of 0.30 mg/kg. However, peak plasma concentrations vary markedly between patients. The area under the concentration-time curve (AUC), and the peak plasma concentrations, are proportional to the dose.

In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Binding to plasma proteins of methylphenidate and its metabolites is low (10-33%). The apparent distribution volume is about 13.1 L/kg.

Biotransformation of methylphenidate is rapid and extensive. Peak plasma concentrations of the main, de-esterified, metabolite, α-phenyl-2-piperidine acetic acid are attained about 2 hours after administration of methylphenidate, and are 30-50 times higher than those of the unchanged substance. The half-life of α-phenyl-2-piperidine acetic acid is about twice that of methylphenidate, and the mean systemic clearance is 0.17 L/h/kg.

Only small amounts of hydroxylated metabolites (eg. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The apparent mean systemic clearance is 10 L/h/kg. After oral administration, 78-97% of the

dose is excreted in the urine and 1-3% in the faeces in the form of metabolites within 48-96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (60-86%).

There are no apparent differences in the pharmacokinetic behaviour of methylphenidate between hyperactive children and normal adults. The elimination data indicate that in patients with normal renal function renal excretion of unchanged methylphenidate would hardly be diminished in the presence of impaired renal function. However, renal excretion of the metabolite α-phenyl-2-piperidine acetic acid may be reduced.

Indications

Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD was previously known as attention-deficit disorder or minimal brain dysfunction in children. Other terms used to describe this behavioural syndrome include: hyperkinetic child syndrome, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children.

Methylphenidate tablets are indicated as part of a comprehensive treatment program which typically includes psychological, education and social measures to stabilise children with a behavioural syndrome characterised by moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10. Non-localising (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations for ADHD:

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires both medical and special psychological, education, and social resources. Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics. Drug treatment is not indicated in all children with symptoms secondary to environmental factors (child abuse in particular) and/or primary psychiatric disorders, including psychosis.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe a stimulant depends on the physician's assessment of the duration and severity of the child's symptoms.

Narcolepsy:

Symptoms include daytime sleepiness, inappropriate sleep episodes, and sudden loss of voluntary muscle tone.

Dosage and Administration

The dosage should be adapted to the patient's needs and responses.

Dose titration
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose. Other strengths of this medicinal product and other methylphenidate-containing products may be available. The maximum daily dosage of methylphenidate is 60 mg.

Adults: For the treatment of narcolepsy administer in divided doses 2 or 3 times daily. The average daily dose is 20-30 mg. Some patients may require 40-60 mg daily. In others 10-15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6pm.

Children (6 years & over): For the treatment of ADHD, try to time administration to coincide with the periods of greatest academic, behavioural or social difficulties. Start with 5 mg once or twice daily (eg. at breakfast and lunch) with gradual increments of 5-10 mg weekly. The total daily dosage should be administered in divided doses. Do not exceed a daily dose of 60 mg.

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.

In some children sleeplessness occurs because the effect of the medicine wears off in the evening. Such children may then rebound to their usual level of activity or distraction. An additional short acting dose of **Methylphenidate** tablets at about 8pm, may solve this problem. Give a trial dose at bedtime to clarify the issue.

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 (see Contraindications and Warnings and Precautions).

Ongoing monitoring:
Growth, psychiatric and cardiovascular status should be continuously monitored (Warnings and Precautions).
• Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
• Height, 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 at least every 6 months and at every visit.

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

Long term (more than 12 months) use in children and adolescents
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication 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 school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Elderly
Methylphenidate 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 should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Contraindications

- Anxiety,
- tension,
- agitation,
- hyperthyroidism,
- Hypersensitivity to methylphenidate or any of its excipients.
- patients with motor tics, tics in siblings or with a family history or diagnosis of Tourette’s syndrome.
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis (see Interactions)
- Hyperthyroidism or thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke.

Warnings and Precautions

Treatment with **Methylphenidate** tablets is not indicated in all cases of Attention-Deficit Hyperactivity disorders, and should be considered only after complete history-taking and evaluation. The decision to prescribe **Methylphenidate** tablets should depend on the

physician's assessment of the duration and severity of symptoms and their appropriateness to the child's age.

Methylphenidate tablets should not be prescribed just because one or more behavioural characteristics is present. When these symptoms are associated with acute stress reactions, treatment with **Methylphenidate** tablets is usually not indicated.

Methylphenidate tablets should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance given in Dosage and Administration and Warnings and Precautions 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 physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication 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 (preferable during school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrthymia) 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 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 may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short and long term clinical consequences of these cardiovasvular 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 Contraindications for conditions in which methylphenidate treatment is contraindicated.

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

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders **unless specialist paediatric advice has been obtained (see Contraindications).**

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, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vunerability 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.

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 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 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 children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate 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 should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

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

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. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. **Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.**

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

Forms of bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with co morbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with co morbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients** (see above 'Psychiatric Disorders' and Dosage and Administration). **Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

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

Methylphenidate 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 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. Available clinical data indicate that treatment with **Methylphenidate** tablets during childhood does not increase the likelihood of adult addiction.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should be taken in to 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 or other stimulants may not be suitable and non-stimulant treatment should be considered.

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

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

Drug screening
This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen tests.

Seizures
Methylphenidate tablets should be used with caution in patients with epilepsy. Clinical experience has shown that a small number of such patients may experience an increase in seizure frequency when treated with **Methylphenidate** tablets. If seizure frequency rises, **Methylphenidate** tablets should be discontinued.

Growth
Although a causal relationship has not been confirmed, moderately reduced weight gain and slight retardation of growth have been reported with long-term use of stimulants 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 weight as expected may need to have their treatment interrupted.

Cerebrovascular disorders:
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.
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 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 therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy

Haematological effects
Data on the safety and efficacy of long term use of **Methylphenidate** tablets are not complete. Patients requiring long term therapy should, therefore be carefully monitored. Periodic complete and differential blood counts and platelet counts are advised during prolonged therapy.

Mutagenicity, Carcinogenicity and Toxicological Studies
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas (a benign tumour) and, in males only, an increase in hepatoblastomas (a malignant tumour) at daily doses of approximately 60 mg/kg/day (about 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis respectively). There is no overall increase in the number of malignant hepatic tumours. The mouse strain used is particularly sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.

Similar studies in F344 rats showed no evidence of carcinogenicity.

Sister chromatid exchange and chromosome aberrations were elevated in an *in vitro* test on cultured ovary cells of Chinese hamster but no mutagenic effects were observed in two further *in vitro* tests (Ames reverse mutation test, mouse lymphoma forward mutation test). In an *in vivo* study of the effect of methylphenidate on mouse bone marrow cells (micronucleus test) in which doses up to 250 mg/kg were given, there was no evidence of clastogenic or aneugenic effects. The strain used for this *in vivo* assay was the B6C3F1 mouse, the same strain that produced a positive response in the mouse carcinogenicity study.

Comment:
The US Food and Drugs Administration examined data from the Surveillance, Epidemiology and End Results (SEER) database for the years 1973 to 1991 and found that the estimated incidence of hepatoblastoma in the general population was not greater than 1 in 10 million person years. On the basis of experience since marketing methylphenidate hydrochloride, there is no evidence that the incidence is higher in patients receiving methylphenidate hydrochloride.

Use during pregnancy and lactation
Class B2 (Prescribing Medicines in Pregnancy 4th edition)
There is a limited amount of data from the use of methylphenidate in pregnant women.

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous reports.

In animal studies, **Methylphenidate** tablets did not affect reproductive performance or fertility and had no embryotoxic, fetotoxic or teratogenic effects at about 2-5 times the therapeutic dose in humans.

Methylphenidate tablets should not be given to pregnant women unless the potential benefit outweighs the risk to the foetus.

Methylphenidate has been found in breast-milk of a women treated with methylphenidate.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with Methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Effects on ability to drive or use machines:
Because **Methylphenidate** tablets may cause dizziness and drowsiness and visual disturbances, patients should be cautioned not to drive, operate machinery, or engage in other potentially dangerous activities if affected.

Adverse Effects

Nervousness and insomnia are the most common adverse reactions. They occur at the beginning of treatment, and can usually be controlled by reducing the dosage and omitting the afternoon or evening dose. Decreased appetite is also common but usually transient.

Frequency of Adverse Effects
Estimates from clinical trails and spontaneous ADR reports, classified as follows:
Frequency estimate:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Nervous system disorders:
Very common: Headache
Common:, Dizziness, dyskinesia, psychomotor hyperactivity, somnolence
Uncommon: Sedation, tremor
Very rare: 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).
Not known: Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions, migraine

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting. Dry mouth.
Uncommon: constipation

Cardiac disorders
Common: arrhythmia, tachycardia, palpitations
Uncommon: chest pain
Rare: angina pectoris
Very rare: cardiac arrest, myocardial infarction
Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Skin and subcutaneous tissue disorders
Common: alopecia, pruritis, rash, urticaria
Uncommon: angioneurotic oedema, bullous conditions, exfoliate conditions
Rare: hyperhidrosis, macular rash, erythema
Very rare: erythema multiforme, exfoliate dermatitis, fixed drug eruption

Blood and lymphatic disorders
Very rare: anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura
Unknown: pancytopenia

Infections and infestations
Common: nasopharyngitis

Immune system disorders
Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders
Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children

Psychiatric disorders
Very common: insomnia, nervousness
Common: anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour
Uncommon: 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
Rare: mania, disorientation, libido disorder
Very rare: suicidal attempt (including completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focusing,
Not known: delusions, thought disturbances, confusional state, dependence.
Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

Eye disorders
Uncommon: diplopia, blurred vision

Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Vascular disorders
Common: hypertension
Very rare: cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Common: cough, pharyngolaryngeal pain
Uncommon: dyspnoea

Hepatobiliary disorders
Uncommon: hepatic enzyme elevations
Very rare: abnormal liver function, including hepatic coma

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia
Uncommon: myalgia, muscle twitching
Very rare: muscle cramps

Renal and urinary disorders
Uncommon: haematuria

Reproductive system and breast disorders
Rare: gynaecomastia

General disorders and administration site conditions
Common: pyrexia, growth retardation during prolonged use in children
Uncommon: chest pain, fatigue
Very rare: sudden cardiac death
Not known: chest discomfort, hyperpyrexia

Investigations
Common: changes in blood pressure and heart rate (usually an increase), weight decreased
Uncommon: cardiac murmur, hepatic enzyme increased
Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

Interactions

Pharmacokinetic interaction
It is not known how methylphenidate may effect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended at combining methylphenidate 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, anticonvulsants (e.g. Phenobarbitol, phenytoin, primodone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting and stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these medicines already being taken and establish medicine plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamics interactions
Anti-hypertensive drugs
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 with other medicines that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Warnings and precautions).

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

Use with alcohol
Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. 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. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extra cellular dopamine levels, methylphenidate 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.

Overdosage

Signs and Symptoms:

Signs and symptoms of acute overdosage, mainly due to overstimulation of the central sympathetic nervous systems, may include: vomiting, agitation, tremor, hyperreflexia, muscle twitching, convulsions (possibly followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment:
Treatment consists in providing supportive measures. Protect the patient from self-injury and external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, the stomach can be evacuated by induction of vomiting or gastric lavage. If intoxication is severe, a carefully titrated dose of a short-acting barbiturate should be given before preforming gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia. The efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdosage of **Methylphenidate** tablets has not been established.

Pharmaceutical Precautions

Store below 30^{o}C. Protect from light and moisture. Shelf life is 3 years.

Medicine Classification

Controlled Drug B2.

Package Quantities

10 mg tablets: Blister packs of 100 tablets

Further Information

Methylphenidate Hydrochloride is 2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride. It has a molecular formula and weight of $C_{14}H_{19}NO_2$.HCl and 269.77 respectively.

Other ingredients of the tablets are: microcrystalline cellulose, lactose, pregelatinised maize starch and stearic acid powder.

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