

Data Sheet

Rubifen
Rubifen SR

Methylphenidate hydrochloride (USP) 5 mg, 10 mg and 20 mg immediate release tablets

Methylphenidate hydrochloride (USP) 20 mg sustained release tablets

Presentation

Rubifen immediate release 5, 10 and 20 mg tablets: round white tablet with slightly bevelled edges, marked RU-5, RU-10 or RU-20 containing 5 mg, 10 mg and 20 mg methylphenidate respectively with a score mark on the 10 mg tablets.

Rubifen sustained release 20 mg tablets: oblong white or white-cream smooth tablet containing 20 mg methylphenidate in a modified release formulation.

Pharmaceutical Form

Tablets for oral administration

Do not halve immediate release tablets. Dose equivalence when the tablet is divided has not been established.

Uses

Actions

Pharmacotherapeutic group: Psychostimulants.

Rubifen is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in humans is not completely understood, but its stimulant effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system. The mechanism by which Rubifen 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.

Pharmacokinetics

Absorption

Immediate release tablets: 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. Peak plasma concentrations vary markedly between patients. The area under the concentration-time curve (AUC) and the peak plasma concentration (C_{max}) are proportional to the dose.

SR Tablets: in the fasted state, absorption of methylphenidate from Rubifen 20 mg SR tablets is 37 % slower than with the conventional tablets and results in a smaller fluctuation of plasma

concentration. C_{max} is lower (by 40 %) and is attained later (at 3 hours) but the total amount absorbed (AUC) is the same.

After a high-fat meal, both AUC (by 25 %) and C_{max} (by 27 %) are significantly higher, although the rate of absorption (C_{max}/AUC ratio) remains the same. Time to C_{max} (T_{max}) is also slightly faster after a high-fat meal (median T_{max} = 2.5 hrs) as compared to without food (median T_{max} = 3 hrs). As with immediate release tablets, there is considerable variation in plasma methylphenidate concentrations between patients.

Distribution

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

Biotransformation

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 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 its 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 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 %).

The elimination half-life and the cumulative urinary excretion of α -phenyl-2-piperidine acetic acid are not significantly different for SR tablets. Hence, in the fasted state, the total amount absorbed from one SR tablet and 20 mg in conventional tablet form is equal.

Characteristics in patients

There are no apparent differences in the pharmacokinetics of methylphenidate between hyperactive children and healthy adult volunteers. Elimination data from patients with normal renal function suggest that 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. Other terms used to describe this behavioural syndrome include: hyperkinetic disorder, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children.

Rubifen is indicated as part of a comprehensive treatment program which typically includes psychological, educational and social measures and is aimed at stabilising 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 central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations for ADHD

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Proper diagnosis requires medical and neuropsychological, educational and social investigation. Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired. 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 this syndrome. Stimulants are not indicated in children with symptoms secondary to environmental factors (child abuse in particular) and/or primary psychiatric disorder, including psychosis. Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms.

Narcolepsy

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

Dosage and Administration

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.

Immediate release tablets

The dosage of Rubifen should be individualised according to the patient's clinical needs and responses. Do not halve tablets. Dose equivalence when the tablet is divided has not been established.

In the treatment of ADHD, an attempt should be made to time administration to coincide with the periods of greatest academic, behavioural and social stress.

Rubifen should be started at a low dose, with increments at weekly intervals. Daily doses above 60 mg are not recommended.

If symptoms do not improve after dose titration over a period of one month, the drug should be discontinued.

If symptoms worsen or other adverse effects occur, the dosage should be reduced or, if necessary, the drug discontinued.

If the effect of the drug wears off too early in the evening, disturbed behaviour and/or inability to go to sleep may recur. A small evening dose of the normal tablet or an afternoon dose of the SR tablet may help to solve this problem.

Rubifen should be discontinued periodically to assess the child's condition. Improvement may continue when the drug is temporarily or permanently discontinued.

Drug treatment should not, and need not, be indefinite. It can usually be discontinued during or after puberty. However, ADHD may continue into adulthood and treatment with Rubifen may be beneficial to those patients after puberty.

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 sections 4.3 and 4.4)

Ongoing monitoring:

Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

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

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 (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

In the treatment of narcolepsy, the usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In hyperactivity disorders in children aged 6 years and over, the usual initial dose is 5 mg once or twice daily by mouth, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses. Methylphenidate may be given before breakfast and lunch. A later dose may be considered if the effect wears off in the evening causing rebound hyperactivity.

Sustained release tablets

Rubifen SR Tablets have a duration of action of about 8 hours. They may therefore be used when a prolonged effect is desired exceeding the duration of action of conventional Rubifen tablets. Rubifen SR tablets must be swallowed whole and never crushed or chewed. Rubifen SR tablets should not be split or divided. They should be taken after meals, preferably after a substantial breakfast (see Pharmacokinetic properties) for maximum duration of effect.

It may be necessary to use a combination of the standard immediate release and SR tablets in some patients to achieve the optimal clinical response. As the duration of action of Rubifen SR tablets is variable from patient to patient, it may not be possible to avoid administration of a Rubifen dose during the middle part of the day in all patients. The total absorption and duration of action of Rubifen SR tablets are maximised when it is taken with a meal.

The total daily dose should be similar to that required if the immediate formulation is used. In the fasted state, Rubifen SR 20 mg gives similar blood concentration to that expected following two Rubifen 10 mg immediate release tablets (with the second being taken four hours after the first).

Contraindications

- Hypersensitivity to methylphenidate or to any of the excipients in Rubifen (see List of Excipients)
- Anxiety, tension, agitation
- Hyperthyroidism
- Glaucoma
- Pheochromocytoma
- Diagnosis of motor tics or tics in siblings with tics
- Diagnosis or family history 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 section 4.5)
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening

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

Long-term use (more than 12 months) 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. 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 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 times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in the elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in 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.

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 arrhythmia,) 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 cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. **Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.**

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

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

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and Cardiovascular Events

Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular Conditions

Patients with pre-existing CNS abnormalities, e.g., cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with Rubifen. Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with Rubifen (see above paragraph on Cardiovascular Conditions and below for Interactions).

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

Psychiatric

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Treatment of ADHD with stimulant products including Rubifen 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.

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.

Psychotic symptoms

Psychotic symptoms, including visual and tactile hallucinations have been reported in patients administered usual prescribed doses of stimulant products, including Rubifen (see Adverse effects). Physicians should consider treatment discontinuation.

Clinical experience suggests that Rubifen may exacerbate symptoms of behavioural disturbance and thought disorder in psychotic children.

Aggressive behaviour

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Rubifen. However, patients with ADHD may experience aggression as part of their medical condition. Therefore causal association with treatment is difficult to assess. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

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

Growth

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

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

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.

Seizures

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

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.

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

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

Withdrawal

Careful supervision is required during drug 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.

Pregnancy-embryonal/foetal development

Methylphenidate is considered to be possibly teratogenic in rabbits. Spina bifida with malrotated hind limbs was observed in two separate litters at a dose of 200 mg/kg/day. This dose was approximately 116-fold higher than the maximum recommended human dose (MRHD) of 60 mg. A second study was conducted with a high dose of 300 mg/kg, which was considered maternally toxic. No spina bifida was seen, however, in 12 litters (92 foetuses) surviving.

Methylphenidate is not teratogenic in rats. Development foetal toxicity was noted at a high dose of 75 mg/kg (44-fold higher than the MRHD) and consisted of an increase of the instance of foetuses with delayed ossification of the skull and hyoid bones as well as foetuses with short supernumerary ribs (see Use During Pregnancy and lactation).

Carcinogenesis-mutagenesis

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 35-fold-higher than the MRHD). There was 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.

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.

A total of 174 cases of hepatoblastoma were reported by the SEER for the period 1973 to 1995. Age-adjusted incidence rate was very low (IR=0,0382 per 100,000 person-years). The majority of the cases (149 out of 174) were diagnosed among the age group 0 to 4 years old, which is in accordance with the natural history of the disease. For the age group 5 to 24 years old the rates of hepatoblastoma were very low with few or no cases reported.

On the basis of experience since marketing Methylphenidate hydrochloride, there is no evidence that the incidence is higher in patients receiving Methylphenidate hydrochloride.

Juvenile neurobehavioural development

Repeated oral administration of methylphenidate to young rats identified decreased spontaneous locomotor activity at 50 mg/kg/day (29-fold higher than the MRHD), due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females and at the highest dose of 100 mg/kg/day (58-fold higher than the MRHD). The clinical relevance of these findings is unknown.

Unlike these preclinical findings, long-term administration of methylphenidate in children with ADHD is well tolerated and improves the school performance. Thus the clinical experience does not suggest that these learning and behavioural results in rats are clinically relevant.

Others

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

The long-term safety of treatment with methylphenidate is not fully known. In the event of Leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Use During Pregnancy [category B2] and Lactation

There is a limited amount of data from the use of methylphenidate in pregnant women.

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

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses.

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Methylphenidate has been found in the breast-milk of a woman 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 and Use Machines

Rubifen may cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It is therefore advisable to exercise caution when driving, operating machinery, or engaging in other potentially hazardous activities.

Adverse Effects

Nervousness and insomnia are very common adverse reactions that occur at the beginning of Rubifen treatment but can usually be controlled by reducing the dosage and/or omitting the afternoon or evening dose.

Decreased appetite is also common but usually transient. Abdominal pain, nausea and vomiting are common, usually occur at the beginning of treatment and may be alleviated by concomitant food intake.

Frequency estimate : very common ≥ 10 %, common ≥ 1 % to < 10 %; uncommon ≥ 0.1 % to < 1 %; rare ≥ 0.01 % to < 0.1 %; very rare < 0.01 %.

Blood and the lymphatic system disorders

Very rare: leucopenia, thrombocytopenia, anaemia

Unknown: pancytopenia

Immune system disorders

Very rare: hypersensitivity Reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutrition 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-focussing,

Not known: delusions thought disturbances, confusional state, dependence.

Nervous system disorders

Common: headache, drowsiness, dizziness, dyskinesia, psychomotor hyperactivity
Uncommon: sedation, tremor

Very rare: convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebral arteritis and/or occlusion migraines

Eye disorders

Uncommon: diplopia, blurred vision,

Rare: difficulties in visual accommodation, visual disturbance, mydriasis

Cardiac disorders

Common: tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase)

Rare: angina pectoris

Very rare: cardiac arrest, myocardial infarction

Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*

Common: hypertension

Uncommon:

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

Respiratory, thoracic and mediastinal disorders

Common: cough, pharyngolaryngeal pain

Uncommon: dyspnoea

Gastrointestinal disorders

Common: abdominal pain, nausea, vomiting, dry mouth

Hepatobiliary disorders

Very rare: Abnormal liver function, ranging from transaminase elevation to hepatic coma

Skin and subcutaneous tissue disorders

Common: rash, pruritus, urticaria, fever, scalp hair loss

Very rare: thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme

Musculoskeletal and connective tissue disorders

Common: arthralgia

Uncommon: myalgia, muscle twitching

Very rare: muscle cramps

General disorders and administration site conditions

Common: slight growth retardation during prolonged use in children.

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

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 drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, 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, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive drugs

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

Use with drugs that elevate blood pressure

Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure

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

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 extracellular 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

Symptoms

Signs and symptoms of acute overdosage, mainly due to overstimulation of the central and 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

Management consists in providing supportive measures, preventing self-injury and protecting the patient from external stimuli that would exacerbate the 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 performing gastric lavage. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external-cooling procedures may be required to reduce hyperpyrexia. The efficacy of peritoneal dialysis or extracorporeal haemodialysis for Rubifen overdosage has not been established.

Pharmaceutical Precautions

Shelf Life: Rubifen 5 mg, 10 mg and 20 mg immediate release: 2 years, Rubifen 20 mg sustained release: 3 years. Protect from moisture and store below 25 °C. Keep out of reach of children.

Incompatibilities: none known

Medicine Classification

Controlled Drug B2.

Package Quantities

Blister packs of 30 tablets.

Further information

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

List of Excipients

Rubifen 5, 10 and 20 mg immediate release tablets: microcrystalline cellulose, maize starch, calcium hydrogen phosphate dihydrate and magnesium stearate.

Rubifen SR 20 mg tablets: cetyl alcohol, ethyl cellulose, anhydrous lactose, magnesium stearate, opadry Y-1-700 (containing hydroxypropyl methylcellulose, polyethylene glycol 400 and titanium dioxide (E-171)).

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