RUBIFEN

COMPOSITION
Per tablet:
Methylphenidate (INN) hydrochloride 10 mg Excipients q.s,

DESCRIPTION:
White round cross-scored tablets, with a central line of fracture. Marked in one side with the anagram RU.10
Diameter of 7.07 mm (* 5%) and thickness of 3.07 mm (± 5%).

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS)
Pharmacodynamics
Methylphenidate is a central nervous stimulant. Its mode of action in humans is not completely understood but methylphenidate presumably exerts its stimulant effect by activating the brainstem arousal system and cortex. There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioural effects in children, nor conclusive evidence as to how these effects relate to the condition of the central nervous system.
The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.
Repeated oral administration of methylphenidate to young rats was associated with decreased spontaneous locomotor activity at systemic exposures (plasma AUC) about 3-fold that at the maximum clinical dose, due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females, at systemic exposures (plasma AUC) 8-fold that at the maximum clinical dose. The clinical relevance of these findings is unknown.

Pharmacokinetics
Absorption:
Following oral administration of Rubifen tablets, the active substance, methylphenidate hydrochloride, is rapidly and almost completely absorbed from the tablets. Owing to extensive first-pass metabolism, its systemic availability amounts to only 30% (11-51 %) of the dose. Ingestion together with food accelerates its absorption but has no influence on the amount absorbed. Peak plasma concentrations of approx. 40 nmol/litre (11 ng/mL) are attained, on the average, 2 hours after administration of 0.30 mg/kg. The peak plasma concentrations, however, vary markedly from one person to another. The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, are proportional to the size of the dose administered.
***Distribution*:**
In the blood, methylphenidate and its metabolites become distributed in the plasma (57%) and the erythrocytes (43%). Methylphenidate and its metabolites have low plasma protein-binding (approximately 15%). The apparent volume of distribution (Vd) has been calculated at 13.1 L/kg after an oral dose. The calculated mean ± SD volume of distribution value after an intravenous dose (V_{ss}) of the racemate in healthy adult volunteers is 2.23 ± 1.01 L/kg.
Metabolism and excretion:
Methylphenidate is eliminated from the plasma with a mean half-life of 2 to 3 hours, and the calculated mean systemic clearance is 4 to 10 L/h/kg after an oral dose. The calculated mean ± SD systemic clearance value after an intravenous dose of the racemate in healthy adult volunteers is 0.565 ± 0.2 L/h/kg. Within 48 to 96 hours, 78 to 97% of the dose administered is excreted in the urine and 1 to 3% in the faeces in the form of metabolites. Unchanged methylphenidate appears in the urine only in small quantities (<1 %). The bulk of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (PPAA, 60 - 86%). Peak plasma concentrations of PPAA are attained about 2 hours after administration of methylphenidate and are 30 to 50 times higher than those of the unchanged substance. The half-life of PPAA is roughly twice as long as that of methylphenidate.
There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and normal adults.

INDICATIONS
Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV): ADHD was previously known as attention-deficit disorder or minimal brain dysfunction. Other terms used to describe this behavioral syndrome include hyperkinetic disorder, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psychoorganic syndrome of children. Rubifen is indicated as part of a comprehensive treatment programme which typically includes psychological, educational and social measures and is aimed at stabilizing children with a behavioural syndrome characterized 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. Nonlocalising (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 aetiology 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 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 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.

CONTRAINDICATIONS

Rubifen is contraindicated in patients with the following:

- Anxiety and tension states
- Agitation,
- Tics
- Tics in siblings
- A family history or diagnosis of Tourette's syndrome.
- Glaucoma
- Hyperthyroidism
- Cardiac arrhythmia
- Severe angina pectoris
- Treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoaminase oxidase inhibitor (hypertensive crises may result).
- Phaeochromocytoma
- Known hypersensitivity to methylphenidate or to any component of the formulation.

PRECAUTIONS

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems Children and Adolescents:

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac 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 drug.

Adults:

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

It is essential that children, adolescents, or adults with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a cardiologist before initiating treatment. Ongoing cardiological supervision should be maintained throughout treatment in these patients.

Cardiovascular Conditions:

Rubifen generally should not be used in patients with severe hypertension. Rubifen increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, and atherosclerosis.

Cardiac arrhythmia and severe angina pectoris are contraindicated (see **Contraindications**). Methylphenidate should be used cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking methylphenidate, especially in those with hypertension.

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

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 “PRECAUTION” – Cardiovascular conditions).

Aggressive behaviour:

Emergent aggressive behaviour or a worsening of baseline aggressive behaviour has been reported during stimulant therapy. 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.

Use in children:
Methylphenidate should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established. Medicines should be kept out of the reach of children.
Depression or Psychosis:
Methylphenidate should not be used as treatment for severe depression of either exogenous or endogenous origin. In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.
Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.
Treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.
Fatigue:
Methylphenidate should not be employed for the prevention or treatment of normal fatigue states.
Seizures:
There is some clinical evidence that methylphenidate may lower the convulsion threshold in patients with a history of seizures, with prior EEG abnormalities in the absence of seizures and, rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, the drug should be discontinued. *Drug dependence:*
As with other stimulants, the possibility of habituation or abuse must be considered, particularly in emotionally unstable patients and those with a history of drug dependence or alcoholism, because such patients may increase the dose on their own initiative.
Alcohol may exacerbate the CNS adverse reactions of psychoactive drugs, including methylphenidate. Therefore, it is advisable for patients to abstain from alcohol during treatment.
Chronic abuse of methylphenidate can lead to marked tolerance and psychic dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially in response to parenteral abuse.
Methylphenidate abuse or dependence does not appear to be a problem in adolescents or adults who were treated with methylphenidate for ADHD as children.
Careful supervision is required during drug withdrawal, since depression as well as the effects of chronic over-activity can be unmasked. Long-term follow-up may be needed for some patients.
Treatment considerations:
Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only in the light of the complete history and evaluation of the child. The decision to prescribe methylphenidate should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness to his or her age. Prescription should not depend solely on the presence of isolated behavioural characteristics. When the symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.
Retardation of growth:
The retardation of growth referred to under ADVERSE REACTIONS is usually followed by catch-up growth when the medication is discontinued. In order to minimize such complications, drug-free periods over weekends, school holidays and long vacations are advocated by some specialists.
Long term use:
Data on safety and efficacy of long-term use of methylphenidate are not complete. Therefore, patients requiring long-term therapy should be carefully monitored.
Laboratory measurements: Periodic complete blood counts, differential and platelet counts are advisable during prolonged therapy.
Effects on ability to drive and use machines:
Methylphenidate may affect the patient's reactions and adversely influence his or her ability to drive and use machines.
Carcinogenicity:
In a lifetime carcinogenicity study carried out in $B6C3F_1$ mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumour type. The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.
Methylphenidate did not cause any increases in tumours in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 50 mg/kg/day, which is approximately 7 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis.
In a 24-week carcinogenicity study in the transgenic mouse strain $p53^{+/-}$, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; approximately 60 and 74 mg/kg/day of methylphenidate, respectively, which is approximately 4 and 5 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis, respectively.
Effects on fertility:
Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 11-fold the highest recommended human dose of methylphenidate on a mg/m^2 basis.

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both paediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation).
Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention

Psychiatric

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/ optimisation and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

USE IN PREGNANCY
Category B3. As a general rule no drugs should be taken during the first 3 months of pregnancy, and the benefits and risks of taking drugs should be carefully considered throughout the whole of the pregnancy.
Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. Oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects at systemic exposures (plasma AUC) approximately 3 times clinical exposure at the maximum recommended human dose. The exposure at the no-effect dose was less than human exposure. In rats, teratogenic effects were not seen at systemic exposures (plasma AUC) approximately 12 times clinical exposure at the maximum recommended human dose.
There are no adequate and well-controlled studies in pregnant women. Therefore, until more information is available, methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

USE IN LACTATION
It is not known whether or not methylphenidate and/or its metabolites pass into breast milk. For safety reasons, mothers taking methylphenidate should refrain from breast-feeding their infants.

INTERACTIONS WITH OTHER DRUGS
Rubifen should be used cautiously with pressor agents and MAO inhibitors due to the risk of severe hypertension. Human pharmacological studies have shown that Rubifen may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, and primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Reduction in the dosage adjustments of these drugs may be required when they are given concomitantly with Rubifen.
In occasional circumstances where guanethidine and methylphenidate are used together, any antihypertensive effect of the former may be attenuated.
Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonist has not been systematically evaluated.

Because a predominant action of methylphenidate is to increase extracellular dopamine levels, Rubifen may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both Rubifen and an antipsychotic, as extrapyramidal symptoms could emerge when these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.

Effects on laboratory tests:
Methylphenidate may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

DOSAGE & ADMINISTRATION:
Dosage should be individualized according to the needs and responses of the patient. In the treatment of ADHD, an attempt should be made to time administration to coincide with periods of greatest academic, behavioural and social stress. Rubifen should be started at a low dose with increments at weekly intervals. Daily doses above 60mg are not recommended. If symptoms do not improve after dose titration over a period of 1 month, Rubifen should be discontinued. If symptoms worsen or other adverse effects occur, the dosage should be reduced or, if necessary, the drug discontinued. If the effects 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 Rubifen 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 after puberty.
Adults
Average dosage is 20 to 30mg daily (one tablet twice or three times a day).
Some patients may require 40-60mg daily, while others, 10-15mg daily will be adequate.
Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.
Children (6 years and over)
Start treatment with 5mg twice a day (before breakfast and lunch), increment gradually 5 to 10mg weekly if necessary. The total daily dosages should be administered in divided doses.

ADVERSE REACTIONS

Post marketing Experience:

Nervousness and insomnia are very common adverse reactions which occur at the beginning of Rubifen treatment and are usually controlled by reducing the dosage and omitting the drug in the afternoon or evening. Decreased appetite is also common but usually transient. In children, loss of appetite, abdominal pain, insomnia and tachycardia may occur more frequently. However, any of the other adverse reactions listed below may also occur.

Adverse reactions listed below are ranked under headings of frequency, using the following convention: 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.

Immune System Disorders:

Very rare: Hypersensitivity reaction

Metabolism and nutrition disorders:

Rare: Moderately reduced weight gain during prolonged use in children

Psychiatric disorders:

Very rare: Hyperactivity, toxic psychosis (sometimes with visual and tactile hallucinations), transient depressed mood.

Nervous system disorders:

Very common: nervousness, insomnia, irritability Common: Headache, drowsiness, dizziness, dyskinesia
Very rare: Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebral arteritis and/or occlusion, reports of poorly documented neuroleptic malignant syndrome

Eye disorders:

Rare: Difficulties in visual accommodation, blurred vision.

Cardiac disorders:

Common: Tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase)
Rare: Angina pectoris.

Gastrointestinal disorders:

Common: Decreased appetite, abdominal pain, nausea, vomiting (which may be alleviated by concomitant food intake), 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
Very rare: Muscle cramps

General disorders and administration site conditions:

Rare: Slight growth retardation during prolonged use in children.

Adverse events reported since market introduction in patients taking methylphenidate include suicide, suicide attempt and suicidal ideation. No causal relationship between methylphenidate and these events has been established.

Post-marketing experience

Reproductive System and Breast Disorders: Priapism

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event. (See Warnings and Precautions)

OVERDOSE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following, vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events, e.g. hypertensive crisis, cardiac arrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the practitioner should consult the Poisons Information Centre or current toxicological publication. 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, further absorption may be limited by administration of activated charcoal. In cases of marked agitation, intravenous doses of diazepam or haloperidol should be given. Hypertension may be controlled by alpha-adrenergic blocking agents or intravenous sodium nitroprusside.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for methylphenidate overdosage has not been established.

PRESENTATION
Rubifen tablets is supplied in boxes of 30 tablets.

STORAGE CONDITIONS
Store below 30°C in a dry place.

SHELF-LIFE
Five years from date of manufacture

KEEP OUT OF REACH FROM CHILDREN
PRESCRIPTION ONLY MEDICAMENT

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LABORATORIOS RUBIÓ, S.A.
(Spain)