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**Methylphenidate HCl
Tablets USP**



**Methylphenidate HCl
Extended-Release
Tablets USP**



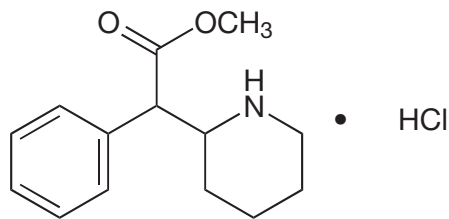
Revised: July 2002

Rx only

DESCRIPTION

Methylphenidate hydrochloride is a mild central nervous system (CNS) stimulant. Methylphenidate hydrochloride is available as 5, 10 and 20 mg tablets for oral administration. A 20 mg extended-release tablet for oral administration is also available.

Methylphenidate hydrochloride is Methyl α -phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular formula is $C_{14}H_{19}NO_2 \cdot HCl$, and its molecular weight is 269.77.

Inactive Ingredients: Methylphenidate hydrochloride tablets: colloidal silicon dioxide, compressible sugar, lactose monohydrate and magnesium stearate. Additionally, the 5 mg contains FD&C Blue #2 and FD&C Red #40; the 10 mg contains FD&C Blue #2 and D&C Yellow #10; and the 20 mg contains FD&C Yellow #6.

Methylphenidate hydrochloride extended-release tablets: anhydrous lactose, cetyl alcohol, ethylcellulose and magnesium stearate.

CLINICAL PHARMACOLOGY:

Methylphenidate is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Methylphenidate hydrochloride in extended-release tablets is more slowly but as extensively absorbed as in the regular tablets. Bioavailability of a methylphenidate hydrochloride extended-release tablet was compared to an extended-release reference product and an immediate-release

product. The extent of absorption for the three products was similar, and the rate of absorption of the two extended-release products was not statistically different.

In a clinical study involving adult subjects who received extended-release tablets, plasma concentrations of methylphenidate hydrochloride's major metabolite appeared to be greater in females than in males. No gender differences were observed for methylphenidate hydrochloride's plasma concentration in the same subjects.

INDICATIONS AND USAGE:

Attention Deficit Disorders, Narcolepsy: *Attention Deficit Disorders* (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Methylphenidate hydrochloride is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (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: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic 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 for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors 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 stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS: Marked anxiety, tension, and agitation are contraindications to methylphenidate hydrochloride, since the drug may aggravate these symptoms. Methylphenidate is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Methylphenidate is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS: Methylphenidate should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Methylphenidate should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of 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.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking methylphenidate, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions: Methylphenidate may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with methylphenidate.

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 agonists has not been systemically evaluated.

Usage in Pregnancy: Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. However, in a recently conducted study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m² basis, respectively. In rats, teratogenic effects were not seen when the drug was given in doses of 75 mg/kg/day, which is approximately 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and a mg/m² basis, respectively. 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.

Drug Dependence: Methylphenidate should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS: Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in 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 for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Long-term effects of methylphenidate in children have not been well established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 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 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively.

Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

ADVERSE REACTIONS: Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have

been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

OVERDOSAGE: 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, and dryness of mucous membranes.

Consult with a Certified Poison Control Center regarding treatment for up-to-date guidance and advice.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

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 hemodialysis for methylphenidate overdosage has not been established.

DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and responses of the patient.

Adults: Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

Extended-Release Tablets: Methylphenidate hydrochloride extended-release tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate hydrochloride extended-release tablets corresponds to the titrated 8-hour dosage of the immediate-release tablets. Methylphenidate hydrochloride extended-release tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over): Methylphenidate hydrochloride tablets should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

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

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

Extended-Release Tablets: Methylphenidate hydrochloride extended-release tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate hydrochloride extended-release tablets corresponds to the titrated 8-hour dosage of the immediate-release tablets. Methylphenidate hydrochloride extended-release tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

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

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED: Methylphenidate Hydrochloride Tablets USP are available as follows:

5 mg: Round, purple, unscored, imprinted "DAN 5" and "5882" supplied in bottles of 100 and 1000.

10 mg: Round, green, scored, imprinted "DAN 10" and "5883" supplied in bottles of 100 and 1000.

20 mg: Round, peach, scored, imprinted "DAN 20" and "5884" supplied in bottles of 100 and 1000.

Protect from light.

Extended-Release, 20 mg: Oval, white to off-white, mottled, unscored, imprinted "WPI" and "3111" supplied in bottles of 30 and 100.

Protect from moisture.

NOTE: Extended-Release tablets are color-additive free.

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

Do not store above 30°C (86°F).

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