CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-300

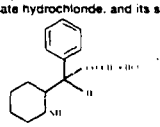
APPROVED DRAFT LABELING

METHYLPHENIDATE HYDROCHLORIDE TABLETS, USP (5 mg, 10 mg, and 20 mg)

C II

DESCRIPTION

Methylphenidate hydrochloride is a mild central nervous system (CNS) stimulant, available as tablets of 5, 10, and 20 mg for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate Hydrochloride

$C_{14}H_{19}NO_2 \cdot HCl$ MW [illegible]

Methylphenidate Hydrochloride USP 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.

Each tablet, for oral administration, contains 5 mg, 10 mg, or 20 mg of methylphenidate hydrochloride. In addition, each tablet contains the following inactive ingredients: Lactose Monohydrate NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, and Talc USP.

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.

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 Tablets are 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, 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.

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, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with methylphenidate.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. 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 charactenstics. 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/m^2 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 increase 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/m^2 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 abdominal 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.

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.

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

Each Methylphenidate Hydrochloride Tablet, USP (5 mg) is available as a round, white unscored tablet debossed with 5 on one side and a [M] on the other side.

Bottles of 100 ..... NDC 0406-1121-01
Bottles of 1000 ..... NDC 0406-1121-10

Each Methylphenidate Hydrochloride Tablet, USP (10 mg) is available as a round, white scored tablet debossed with 10 on one side of the tablet and a [M] on the other side.

Bottles of 100 ..... NDC 0406-1122-01
Bottles of 1000 ..... NDC 0406-1122-10

Each Methylphenidate Hydrochloride Tablet, USP (20 mg) is available as a round, white scored tablet debossed with 20 on one side of the tablet and a [M] on the other side.

Bottles of 100 ..... NDC 0406-1124-01
Bottles of 1000 ..... NDC 0406-1124-10

Protect from light. Dispense in tight, light-resistant container with child-resistant closure.
Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture.
Rx only.

Manufactured by
Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.

SPECIMEN

MALLINCKRODT

Printed in U.S.A.

7/98

NDC 0406-1124-01

METHYLPHENIDATE HYDROCHLORIDE C II

TABLETS, USP

20 mg

Each tablet contains:
Methylphenidate Hydrochloride, USP...20 mg
Rx only.

100 TABLETS

MALLINCKRODT

27 10[illegible]

USUAL DOSAGE:
See package insert.

STORAGE: Store at controlled room temperature 15° to 30°C (59° to 86°F).

Protect from light.

Dispense in a tight, light-resistant container with a child-resistant closure.

Mallinckrodt Inc.
St. Louis, MO 63134, U.S.A.

FPO
0406-1124-01
Rev. 7/98

SPECIMEN

NDC 0406-1121-01

METHYLPHENIDATE HYDROCHLORIDE C II

TABLETS, USP

5 mg

Each tablet contains:
Methylphenidate Hydrochloride, USP...5 mg
Rx only.

NOV 27 1998

100 TABLETS

MALLINCKRODT

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NOV 27 19[illegible]

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SPECIMEN

NDC 0406-1121-10

METHYLPHENIDATE HYDROCHLORIDE C II

TABLETS, USP

5 mg

Each tablet contains:
Methylphenidate Hydrochloride, USP..... 5 mg
This package is not for household use.
Rx only.

1000 TABLETS

MALLINCKRODT

USUAL DOSAGE:
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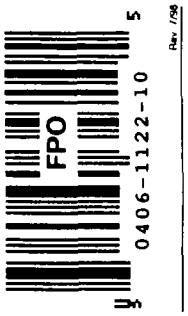

SPECIMEN

NDC 0406-1124-10

METHYLPHENIDATE HYDROCHLORIDE

C II

TABLETS, USP

20 mg

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Methylphenidate Hydrochloride, USP..... 20 mg
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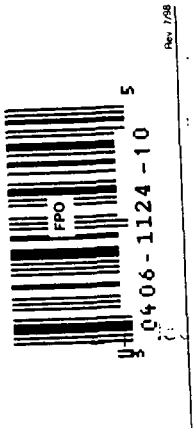

SPECIMEN