

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-475

APPROVED LABELING

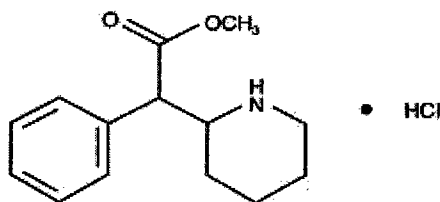
Methylin® Chewable Tablets
(methylphenidate HCl chewable tablets)
2.5 mg, 5 mg and 10 mg



Rx only

DESCRIPTION

Methylin® (methylphenidate HCl) is a mild central nervous system (CNS) stimulant, available as 2.5 mg, 5 mg and 10 mg chewable tablets 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 = 269.77

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 Methylin® Chewable Tablet, for oral administration, contains 2.5 mg, 5 mg or 10 mg of Methylphenidate Hydrochloride, USP. In addition, Methylin® Chewable Tablets also contain the following inactive ingredients: Aspartame NF, Maltose, Microcrystalline Cellulose NF, Guar Gum NF, Grape Flavor, Pregelatinized Starch NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo enantiomers. The *d*-threo enantiomer is more pharmacologically active than the *l*-threo enantiomer.

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

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

Pharmacokinetics:

Absorption

Methylin® Chewable Tablets are readily absorbed. Following oral administration of Methylin® Chewable Tablets, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin® Chewable Tablets have been shown to be bioequivalent to Ritalin® tablet. The mean C_{max} following a 20 mg dose is approximately 10 ng/mL.

Food Effect:

In a study in adult volunteers investigating the effects of a high-fat meal on the bioavailability of Methylin[®] Chewable Tablets at a dose of 20 mg, the presence of food delayed the peak concentrations by approximately 1 hour (1.5 hours, fasted and 2.4 hours, fed). Overall, a high-fat meal increased the AUC of Methylin[®] Chewable Tablets by about 20%, on average. Through a cross-study comparison, the magnitude of food effect is found to be comparable between the Methylin[®] Chewable Tablets and Ritalin[®], the immediate release tablet.

Metabolism and Excretion:

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

The pharmacokinetics of the Methylin[®] Chewable Tablets have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20 mg Methylin[®] Chewable Tablets ($t_{1/2} = 3$ hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2} = 2.8$ hours) in healthy adult volunteers.

Special Populations:

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin[®] Chewable Tablets administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin[®] Chewable Tablets administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin[®] Chewable Tablets administration have not been studied in pediatrics.

Renal Insufficiency:

There is no experience with the use of Methylin[®] Chewable Tablets in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin[®] Chewable Tablets.

Hepatic Insufficiency:

There is no experience with the use of Methylin[®] Chewable Tablets in patients with hepatic insufficiency.

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.

Methylin[®] 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 Methylin[®], since the drug may aggravate these symptoms. Methylin[®] 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.

Methylin[®] 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

Methylin[®] 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 Methylin[®] 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.

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

Methylin[®] should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Methylin[®] 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 Methylin[®] 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 Methylin[®], especially those with hypertension.

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

PRECAUTIONS

General

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 Methylin® 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 Methylin® is usually not indicated.

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

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Methylin®:

Choking: Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention.

Directions: Take this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.

Phenylketonurics: Phenylalanine is a component of aspartame. Each 2.5 mg Methylin® Chewable Tablet contains 0.42 mg of phenylalanine; each 5.0 mg Methylin® Chewable Tablet contains 0.84 mg of phenylalanine and each 10.0 mg Methylin® Chewable Tablet contains 1.68 mg of phenylalanine.

Drug Interactions

Methylin® may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that Methylin® 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 Methylin®. 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.

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 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/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.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Methylin[®] 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.

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.

DRUG ABUSE AND DEPENDENCE

Methylin[®] 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.

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.

Directions: Take this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.

Adults

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)

Methylin[®] 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.

Chewable 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.

Methylin[®] 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 Methylin[®] Chewable Tablet 2.5 mg is available as a white to cream colored, grape flavored rounded square tablet with a convex surface, debossed with a "2.5" and "CHEW" below it on one side, and a raised "M" in a debossed square box on the other side.

Bottles of 30.....NDC 0406-1132-03

Bottles of 100.....NDC 0406-1132-01

Bottles of 1000.....NDC 0406-1132-10

Each Methylin® Chewable Tablet 5 mg is available as a white to cream colored, grape flavored rounded square tablet with a convex surface, debossed with a “5” and “CHEW” below it on one side, and a raised “M” in a debossed square box on the other side.

Bottles of 30.....NDC 0406-1135-03

Bottles of 100.....NDC 0406-1135-01

Bottles of 1000.....NDC 0406-1135-10

Each Methylin® Chewable Tablet 10 mg is available as a white to cream colored, grape flavored, scored rounded square tablet with a convex surface, debossed with a “10” and “CHEW” below it on one side, and a raised “M” in a debossed square box on the other side.

Bottles of 30.....NDC 0406-1137-03

Bottles of 100.....NDC 0406-1137-01

Bottles of 1000.....NDC 0406-1137-10

Protect from moisture. Dispense in tight container with child-resistant closure.

Storage: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

The “M” in a debossed square box is a registered trademark of Mallinckrodt Inc.

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St. Louis, MO 63134 U.S.A

tyco/Healthcare

Mallinckrodt

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(ATTACHMENT TO FDA APPROVAL LETTER FOR NDA 21-475)