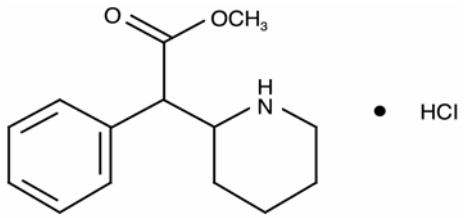
CII

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

$C_{14}H_{19}NO_2 \bullet HCl$ **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 ($t_{½}$) of methylphenidate following administration of 20 mg Methylin® Chewable Tablets ($t_{½}$ = 3 hours) is comparable to the mean terminal $t_{½}$ following administration of Ritalin® (methylphenidate hydrochloride immediate-release tablets) ($t_{½}$ = 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

Serious Cardiovascular Events

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 deaths, 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.

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. 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, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

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 (e.g., electrocardiogram and echocardiogram). 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.

Psychiatric Adverse Events

Pre-Existing Psychosis - Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness - 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. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms - 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. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression - Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

USE IN CHILDREN LESS THAN SIX YEARS OF AGE

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

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.

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/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 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.

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/m^2 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/m^2 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 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.

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 debossed ʌ on the other side.

Bottles of 100.....NDC 68188-132-01

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 debossed ʌ on the other side.

Bottles of 100.....NDC 68188-135-01

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 debossed ʌ on the other side.

Bottles of 100.....NDC 68188-137-01

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

Storage: Store at 20º to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Methylin® is a registered trademark of Mallinckrodt Inc.

Ritalin® is a registered trademark of Novartis Pharmaceuticals Corp.

Manufactured for:
Alliant Pharmaceuticals, Inc.
333 North Point Center East, Suite 250
Alpharetta, Georgia 30022 U.S.A.

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

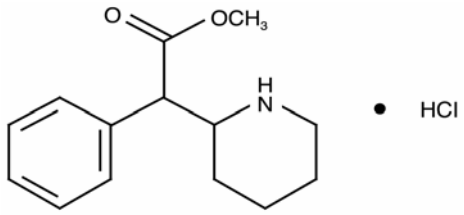
Rev 052406

CII

Methylin® Oral Solution
methylphenidate HCl oral solution, 5 mg/5 mL
methylphenidate HCl oral solution, 10 mg/5 mL
Rx only

DESCRIPTION

Methylin® methylphenidate HCl oral solution, is a mild central nervous system (CNS) stimulant, available as 10 mg/5 mL and 5 mg/5 mL oral solutions for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate Hydrochloride

$C_{14}H_{19}NO_2 \bullet HCl$ 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 mL of Methylin® Oral Solution 5 mg/5 mL contains 1 mg of Methylphenidate Hydrochloride, USP.

Each mL of Methylin® Oral Solution 10 mg/5 mL contains 2 mg of Methylphenidate Hydrochloride, USP.

In addition, Methylin® Oral Solution also contains the following inactive ingredients: Citric Acid Anhydrous USP, Glycerin USP, N&A Grape Flavor, PEG 1450 NF, and Purified Water USP.

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.

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Food Effect

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of Methylin® Oral Solution at a dose of 20 mg, the presence of food delayed the peak by approximately 1 hour (1.7 hours, fasted and 2.7 hours, fed). Overall, a high-fat meal increased the C_{max} of Methylin® Oral Solution by about 13% and the AUC by about 25%, on average. Through a cross-study comparison, the magnitude of increase in C_{max} and AUC is found to be comparable between the Methylin® Oral Solution and Ritalin®, the immediate release tablet.

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The pharmacokinetics of the Methylin® Oral Solution have been studied in healthy adult volunteers. The mean terminal half-life ($t_{½}$) of methylphenidate following administration of 20 mg Methylin® ($t_{½}$ = 2.7 hours) is comparable to the mean terminal $t_{½}$ following administration of Ritalin® (methylphenidate hydrochloride immediate-release tablets) ($t_{½}$ = 2.8h) in healthy adult volunteers.

Special Populations

Gender - The effect of gender on the pharmacokinetics of methylphenidate after Methylin® Oral Solution administration has not been studied.

Race - The influence of race on the pharmacokinetics of methylphenidate after Methylin® Oral Solution administration has not been studied.

Age - The pharmacokinetics of methylphenidate after Methylin® Oral Solution administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin® Oral Solution 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® Oral Solution.

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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.

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Psychiatric Adverse Events

Pre-Existing Psychosis - Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness - 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. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms - 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. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression - Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e.,

treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

USE IN CHILDREN LESS THAN SIX YEARS OF AGE

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

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.

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 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.

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/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 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.

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 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

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.

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

Methylin® Oral Solution 5 mg per 5 mL is available as a colorless, grape flavored liquid.

Bottles of 500 mL .....NDC 68188-881-50

Methylin® Oral Solution 10 mg per 5 mL is available as a colorless, grape flavored liquid.

Bottles of 500 mL .....NDC 68188-882-50

Dispense in tight container with child-resistant closure.

Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Methylin® is a registered trademark of Mallinckrodt Inc.

Ritalin® is a registered trademark of Novartis Pharmaceuticals Corp.

Manufactured for:
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Alpharetta, Georgia 30022 U.S.A.

Manufactured by:
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Patient Information Leaflet

METHYLIN® ORAL SOLUTION **CII**
(methylphenidate hydrochloride oral solution)
Rx only

INFORMATION FOR PATIENTS OR THEIR PARENTS OR CAREGIVERS

Please read this leaflet before you start taking Methylin® Oral Solution. Read the accompanying leaflet each time you get a new prescription of Methylin® Oral Solution. There may be new information. This leaflet provides a summary of information about Methylin® Oral Solution, but does not take the place of your doctor's instructions. If you have any questions or concerns, or want more information about Methylin® Oral Solution, talk to your doctor or pharmacist.

What is Methylin® Oral Solution?

Methylin® Oral Solution is a part of a total treatment program for Attention Deficit Hyperactivity Disorder, or ADHD. Methylin® Oral Solution contains methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. Methylin® is available in several forms including Methylin® Oral Solution which is available in 2 strengths, as 10 mg in each 5 mL of solution and 5 mg in each 5 mL of solution.

Ingredients in Methylin® Oral Solution:
Active ingredient: Methylphenidate Hydrochloride, USP.
Inactive ingredients: Citric Acid Anhydrous USP; Glycerin USP; N&A Grape Flavor, PEG 1450 NF; and Purified Water USP.

What is Attention Deficit Hyperactivity Disorder, ADHD?

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, daytime drowsiness, slow processing of information, difficulty learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low self-esteem, and excessive effort to maintain some organization. The symptoms shown by adults who primarily have attention problems, but not hyperactivity have been commonly described as Attention-Deficit Disorder (ADD).

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

Methylphenidate, the active ingredient in Methylin® Oral Solution, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

BEFORE BEGINNING METHYLIN® ORAL SOLUTION TREATMENT

It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that Methylin® Oral Solution is only part of the overall management of ADHD. Parents, teachers, physicians and other professionals are part of a team that must work together.

Before Methylin® Oral Solution treatment, your doctor should be made aware of any current or past physical or mental problems. Tell your doctor if there is a history of drug or alcohol abuse, depression, psychosis, epilepsy or seizure disorders, high blood pressure, glaucoma, facial tics (involuntary movements), or a family history of Tourette's syndrome.

What should I discuss with my doctor before taking Methylin® Oral Solution?

Talk to your doctor ***before*** taking Methylin® Oral Solution if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's Syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have an abnormal heart rate or rhythm.

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking Methylin® Oral Solution.

Both your doctor and your pharmacist should also be informed of all medicines that you are taking, even if these drugs are not taken on a regular basis and are available without prescription. Your doctor will decide whether you can take Methylin® Oral Solution with other medicines. Methylphenidate is known to interact with a number of other drugs. These include medicines to treat depression, such as monoamine oxidase inhibitors; to control seizures; and to thin blood. Sometimes these interactions may require a change in dosage, or occasionally stopping one of the drugs involved.

Tell your doctor if you are pregnant or nursing a baby.

Can I take Methylin® Oral Solution with other medicines?

Tell your doctor about all medicines that you are taking or intend to take. Your doctor should decide whether you can take Methylin® Oral Solution with other medicines. These include:

- Other medicines that a doctor has prescribed.
- All medicines that you buy yourself without a prescription.
- Any herbal remedies that you may be taking.

Monoamine Oxidase (MAO) Inhibitors - A MAO inhibitor is a medicine sometimes used for depression and other mental problems. You should not take Methylin® Oral Solution with MAO inhibitors or within 14 days of stopping a MAO inhibitor.

Starting a new Medicine - While on Methylin® Oral Solution, do not start taking a new medicine or herbal remedy before checking with your doctor.

Other Medicines You May Be Taking - Methylin® Oral Solution may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with Methylin® Oral Solution.

Who should NOT take Methylin® Oral Solution?

Do NOT take Methylin® Oral Solution if:

- You have significant anxiety, tension, or agitation since Methylin® Oral Solution may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in Methylin® Oral Solution.
- You have glaucoma, an eye disease.
- You have tics or Tourette's Syndrome, or a family history of Tourette's Syndrome.
- You are taking a monoamine oxidase inhibitor, a type of drug, or have discontinued a monoamine oxidase inhibitor in the last 14 days.

Talk to your doctor if you believe any of these conditions apply to you.

WHILE TAKING METHYLIN® ORAL SOLUTION

How To Take Methylin® Oral Solution:

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

Methylin® Oral Solution should preferably be taken 30 to 45 minutes before meals.

Possible side effects of Methylin® Oral Solution:

The most common side effects of Methylin® Oral Solution are:

- Nervousness
- Stomach pain
- Sleeplessness
- Decreased appetite.

Other side effects seen with methylphenidate, the active ingredient in Methylin® Oral Solution, include nausea, vomiting, dizziness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

Dependence - Abuse of methylphenidate can lead to dependence. Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Blurred Vision - Tell your doctor if you have blurred vision when taking Methylin® Oral Solution. This could be a sign of a serious problem.

Slower Growth - Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gain in weight as your doctor expects, your doctor may stop your Methylin® Oral Solution treatment.

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

Other Important Safety Information

Pregnancy and Nursing - Before taking Methylin® Oral Solution, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Overdose - Call your doctor immediately if you take more than the amount of Methylin® Oral Solution prescribed by your doctor.

Methylin® Oral Solution has not been studied in children under 6 years of age.

Methylin® Oral Solution may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share Methylin® Oral Solution with anyone else and take only the amount of Methylin® Oral Solution prescribed by your doctor.

Storage and General Advice

Methylin® Oral Solution should be stored in a safe place at room temperature (between 59° to 86°F). Do not store this medicine in hot, damp, or humid places. Keep the container of Methylin® Oral Solution in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication. Keep track of the volume so that you will know if any is missing.

Someone who has easy access to Methylin® Oral Solution may be able to give it to others or misuse the medication. Do not use Methylin® Oral Solution for a condition for which it was not prescribed.

Keep out of the reach of children.

This leaflet summarizes the most important information about Methylin® Oral Solution. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Methylin® Oral Solution that is written for health professionals.

Prepared by Mallinckrodt Inc.

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