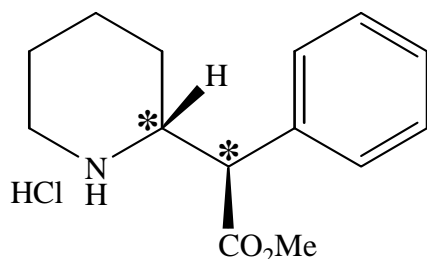


Dexmethylphenidate Hydrochloride Tablets

Rx only

DESCRIPTION

Dexmethylphenidate Hydrochloride is the *d-threo*- enantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of the *d-threo*- and *l-threo*- enantiomers. Dexmethylphenidate Hydrochloride is a central nervous system (CNS) stimulant, available in three tablet strengths. Each tablet contains dexmethylphenidate hydrochloride 2.5, 5, or 10 mg for oral administration. Dexmethylphenidate hydrochloride is methyl α -phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its empirical formula is $C_{14}H_{19}NO_2 \cdot HCl$. Its molecular weight is 269.77 and its structural formula is:



Note: * = asymmetric carbon centers

Dexmethylphenidate hydrochloride is a white to off white 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.

Dexmethylphenidate Hydrochloride also contains the following inert ingredients: pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C Blue No.1 #5516 aluminum lake (2.5 mg tablets), D&C Yellow Lake #10 (5 mg tablets); the 10 mg tablet contains no dye.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Dexmethylphenidate hydrochloride is a central nervous system stimulant. Dexmethylphenidate Hydrochloride, the more pharmacologically active enantiomer of the *d*- and *l*-enantiomers, 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. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

Pharmacokinetics

Absorption

Dexmethylphenidate hydrochloride is readily absorbed following oral administration of Dexmethylphenidate Hydrochloride. In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum in the fasted state at about 1 to 1½ hours post-dose. No differences in the pharmacokinetics of Dexmethylphenidate Hydrochloride were noted following single and repeated twice daily dosing, thus indicating no significant drug accumulation in children with ADHD.

When given to children as capsules in single doses of 2.5 mg, 5 mg, and 10 mg, C_{max} and AUC_{0-inf} of dexamethylphenidate were proportional to dose. In the same study, plasma dexamethylphenidate levels were comparable to those achieved following single *dl-threo*-methylphenidate HCl doses given as capsules in twice the total mg amount (equimolar with respect to Dexamethylphenidate Hydrochloride).

Food Effects

In a single dose study conducted in adults, coadministration of 2x10 mg Dexamethylphenidate Hydrochloride with a high fat breakfast resulted in a dexamethylphenidate t_{max} of 2.9 hours post-dose as compared to 1.5 hours post-dose when given in a fasting state. C_{max} and AUC_{0-inf} were comparable in both the fasted and non-fasted states.

Distribution

Plasma dexamethylphenidate concentrations in children decline exponentially following oral administration of Dexamethylphenidate Hydrochloride.

Metabolism and Excretion

In humans, dexamethylphenidate is metabolized primarily to *d*- α -phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. This metabolite has little or no pharmacological activity. There is little or no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of minute levels of *l-threo*-methylphenidate being detectable in a few samples in only 2 of 58 children and adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose.

In vitro studies showed that dexamethylphenidate did not inhibit cytochrome P450 isoenzymes.

The mean plasma elimination half-life of dexamethylphenidate is approximately 2.2 hours.

Special Populations

Gender

Pharmacokinetic parameters were similar for boys and girls (mean age 10 years).

In a single dose study conducted in adults, the mean dexamethylphenidate AUC_{0-inf} values (adjusted for body weight) following single 2 x 10 mg doses of Dexamethylphenidate Hydrochloride were 25-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both t_{max} and $t_{1/2}$ were comparable for males and females.

Race

There is insufficient experience with the use of Dexamethylphenidate Hydrochloride to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of dexamethylphenidate after Dexamethylphenidate Hydrochloride administration have not been studied in children less than 6 years of age. When single doses of Dexamethylphenidate Hydrochloride were given to children between the ages of 6 to 12 years and healthy adult volunteers, C_{max} of dexamethylphenidate was similar, however children showed somewhat lower AUCs compared to the adults.

Renal Insufficiency

There is no experience with the use of Dexmethylphenidate Hydrochloride in patients with renal insufficiency. After oral administration of radiolabeled racemic 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 very little unchanged drug is excreted in the urine, renal insufficiency is expected to have little effect on the pharmacokinetics of Dexmethylphenidate Hydrochloride.

Hepatic Insufficiency

There is no experience with the use of Dexmethylphenidate Hydrochloride in patients with hepatic insufficiency.

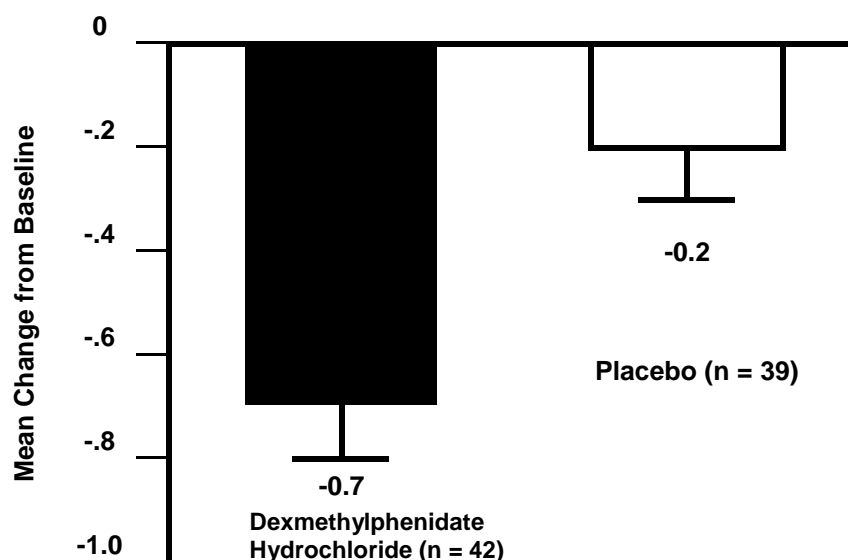
(For Drug Interactions, see Precautions)

Clinical Studies

Dexmethylphenidate Hydrochloride was evaluated in two double-blind, parallel-group, placebo-controlled trials in untreated or previously treated patients aged 6 to 17 years old with a DSM-IV diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Both studies included all three subtypes of ADHD, i.e., Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type. While both children and adolescents were included, the sample was predominantly children, thus, the findings are most pertinent to this age group. In both studies, the primary comparison of interest was Dexmethylphenidate Hydrochloride *versus* placebo.

Dexmethylphenidate Hydrochloride (5, 10, or 20 mg/day total dose), *dl-threo*-methylphenidate HCl (10, 20, or 40 mg/day total dose), and placebo were compared in a multicenter, 4-week, parallel group study in n=132 patients. Patients took the study medication twice daily, 3.5 to 5.5 hours between doses. Treatment was initiated with the lowest dose, and doses could be doubled at weekly intervals, depending on clinical response and tolerability, up to the maximum dose. The change from baseline to week 4 of the averaged score (an average of two ratings during the week) of the teacher's version of the SNAP-ADHD Rating Scale, a scale for assessing ADHD symptoms, was the primary outcome. Patients treated with Dexmethylphenidate Hydrochloride showed a statistically significant improvement in symptom scores from baseline over patients who received placebo.

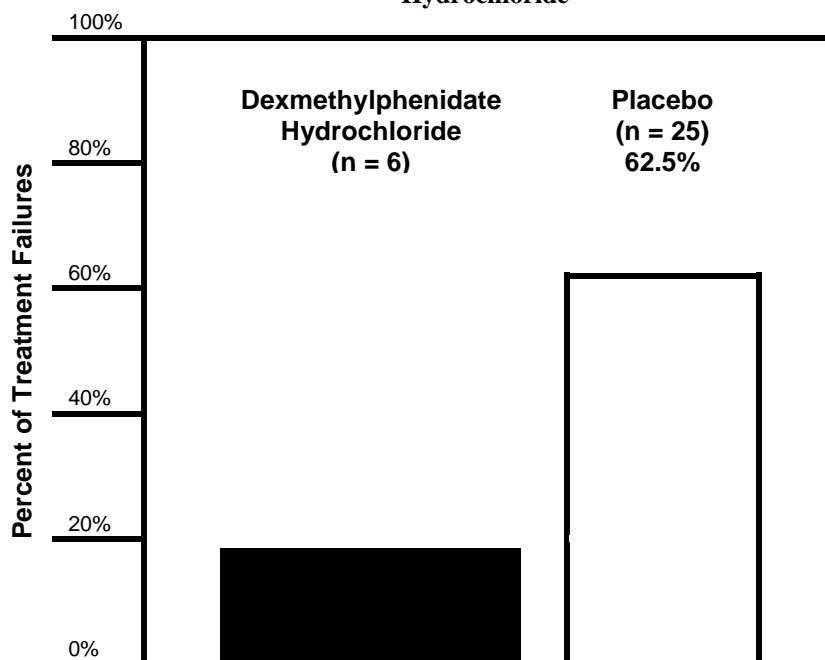
Figure 1
Mean Change from Baseline in Teacher SNAP-ADHD
Scores in a 4-week Double-blind Placebo-controlled
Study of Dexmethylphenidate Hydrochloride*



*Figure 1: Error bars represent the standard error of the mean.

The other study, involving n=75 patients, was a multicenter, placebo-controlled, double-blind, 2-week treatment withdrawal study in children who were responders during a 6-week, open label initial treatment period. Children took study medication twice a day separated by a 3.5 to 5.5 hour interval. The primary outcome was proportion of treatment failures at the end of the 2-week withdrawal phase, where treatment failure was defined as a rating of 6 (much worse) or 7 (very much worse) on the Investigator Clinical Global Impression –Improvement (CGI-I). Patients continued on Dexmethylphenidate Hydrochloride showed a statistically significant lower rate of failure over patients who received placebo.

Figure 2
Percent of Treatment Failures following a 2-week Double-blind Placebo-controlled Withdrawal of Dexmethylphenidate Hydrochloride



INDICATION AND USAGE

Dexmethylphenidate Hydrochloride is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Dexmethylphenidate Hydrochloride in the treatment of ADHD was established in two controlled trials of patients aged 6 to 17 years of age who met DSM-IV criteria for ADHD (See Clinical Studies).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the inattentive type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; “on the go”; excessive talking; blurting answers; can’t wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

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. 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 the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

Dexmethylphenidate Hydrochloride is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. 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 patient's symptoms.

Long-term Use

The effectiveness of Dexmethylphenidate Hydrochloride for long-term use, *i.e.*, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Dexmethylphenidate Hydrochloride for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

CONTRAINDICATIONS**Agitation**

Dexmethylphenidate Hydrochloride is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

Dexmethylphenidate Hydrochloride is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

Dexmethylphenidate Hydrochloride is contraindicated in patients with glaucoma.

Tics

Dexmethylphenidate Hydrochloride is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see Adverse Reactions).

Monoamine Oxidase Inhibitors

Dexmethylphenidate Hydrochloride 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

Depression

Dexmethylphenidate Hydrochloride should not be used to treat severe depression.

Fatigue

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

Long-Term Suppression of Growth

Sufficient data on safety of long-term use of Dexmethylphenidate Hydrochloride 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. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Hypertension and Other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Dexmethylphenidate Hydrochloride, especially those with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both Dexmethylphenidate Hydrochloride and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mmHg, compared to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g.*, those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

Visual Disturbance

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

Use in Children Under 6 Years of Age

Dexmethylphenidate Hydrochloride should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE: Dexmethylphenidate Hydrochloride should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

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

Information for Patients

Patient information is printed at the end of this insert. To assure safe and effective use of Dexmethylphenidate Hydrochloride, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Because of possible effects on blood pressure, Dexmethylphenidate Hydrochloride should be used cautiously with pressor agents.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (*e.g.*, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant 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 systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic 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. 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.

Racemic 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.

In a 24-week study of racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60 to 74 mg/kg/day of racemic methylphenidate.

Dexmethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, or the *in vivo* mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day.

Pregnancy

Pregnancy Category C

In studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels (AUCs) of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with the maximum recommended human dose of 20 mg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. Dexmethylphenidate Hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Dexmethylphenidate Hydrochloride is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Dexmethylphenidate Hydrochloride in children under 6 years old have not been established. Long-term effects of Dexmethylphenidate Hydrochloride in children have not been well established (see Warnings).

ADVERSE REACTIONS

The pre-marketing development program for Dexmethylphenidate Hydrochloride included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received Dexmethylphenidate Hydrochloride 5, 10, or 20 mg/day. The 684 ADHD patients (ages 6 to 17 years) were evaluated in two controlled clinical studies, two clinical pharmacology studies, and two uncontrolled long-term safety studies. Safety data on all patients are included in the discussion that

follows. Adverse reactions were assessed by collecting adverse events, and results of physical examinations, vital sign and body weight measurements, and laboratory analyses.

Adverse events during exposure were primarily obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with Dexmethylphenidate Hydrochloride

Adverse Events Associated with Discontinuation of Treatment

No Dexmethylphenidate Hydrochloride-treated patients discontinued due to adverse events in two placebo-controlled trials. Overall, 50 of 684 children treated with Dexmethylphenidate Hydrochloride (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

Adverse Events Occurring at an Incidence of 5% or More Among Dexmethylphenidate Hydrochloride-Treated Patients

Table 1 enumerates treatment-emergent adverse events for two, placebo-controlled, parallel group trials in children with ADHD at Dexmethylphenidate Hydrochloride doses of 5, 10, and 20 mg/day. The table includes only those events that occurred in 5% or more of patients treated with Dexmethylphenidate Hydrochloride where the incidence in patients treated with Dexmethylphenidate Hydrochloride was at least twice the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Treatment-emergent Adverse Events¹ Occurring During Double-Blind Treatment in Clinical Trials of Dexmethylphenidate Hydrochloride

Body System	Preferred Term	Dexmethylphenidate Hydrochloride	
		Placebo (n=79)	(n=82)
Body as a Whole	Abdominal Pain	15%	6%
	Fever	5%	1%
Digestive System	Anorexia	6%	1%
	Nausea	9%	1%

1 Events, regardless of causality, for which the incidence for patients treated with Dexmethylphenidate Hydrochloride was at least 5% and twice the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. 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 below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased

Gastrointestinal: nausea

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood

Skin/subcutaneous: 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

Controlled Substance Class

Dexmethylphenidate Hydrochloride, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS 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.

Recommended Treatment

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 as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. 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 for Dexmethylphenidate Hydrochloride overdose has not been established.

Poison Control Center

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdose with methylphenidate.

DOSAGE AND ADMINISTRATION

Dexmethylphenidate Hydrochloride is administered twice daily, at least 4 hours apart. Dexmethylphenidate Hydrochloride may be administered with or without food.

Dosage should be individualized according to the needs and responses of the patient.

Patients New to Methylphenidate

The recommended starting dose of Dexmethylphenidate Hydrochloride for patients who are not currently taking racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day (2.5 mg twice daily).

Dosage may be adjusted in 2.5 to 5 mg increments to a maximum of 20 mg/day (10 mg twice daily). In general, dosage adjustments may proceed at approximately weekly intervals.

Patients Currently Using Methylphenidate

For patients currently using methylphenidate, the recommended starting dose of Dexmethylphenidate Hydrochloride is half the dose of racemic methylphenidate. The maximum recommended dose is 20 mg/day (10 mg twice daily).

Maintenance/Extended treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Dexmethylphenidate Hydrochloride. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Dexmethylphenidate Hydrochloride for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

HOW SUPPLIED

Tablets, D-shaped, embossed "D" on upper convex face and dosage strength on lower convex face

Tablets 2.5 mg - blue
Bottles of 100.....NDC 0078-0380-05

Tablets 5 mg - yellow
Bottles of 100.....NDC 0078-0381-05

Tablets 10 mg - white
Bottles of 100.....NDC 0078-0382-05

Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F).

[see USP Controlled Room Temperature]

Protect from light and moisture.

REFERENCE

American Psychiatric Association. *Diagnosis and Statistical Manual of Mental Disorders*. 4th ed. Washington DC: American Psychiatric Association 1994.

Rx Only

Manufactured by Mikart, Inc. (Atlanta, GA) for Novartis Pharmaceutical Corporation.

INFORMATION FOR PATIENTS TAKING DEXMETHYLPHENIDATE HYDROCHLORIDE OR FOR THEIR PARENTS OR CAREGIVERS

Dexmethylphenidate hydrochloride Rx only CII

This information for patients or their parents or caregivers is about Dexmethylphenidate Hydrochloride, a medication intended for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Please read this before you start taking Dexmethylphenidate Hydrochloride. It is not intended to replace your doctor's instructions or advice. If you have any questions about this material or about Dexmethylphenidate Hydrochloride, be sure to talk to your doctor or pharmacist.

What is Dexmethylphenidate Hydrochloride?

Dexmethylphenidate Hydrochloride is a central nervous system stimulant for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Dexmethylphenidate hydrochloride, the active ingredient of Dexmethylphenidate Hydrochloride, is also found in methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. Dexmethylphenidate Hydrochloride is available in a D-shaped tablet form, 2.5 mg, 5 mg, and 10 mg, and is intended to be used in doses of 5 to 20 mg per day, given as divided doses, as directed by your doctor.

What is Attention Deficit Hyperactivity Disorder (ADHD)?

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder characterized by symptoms of inattentiveness and/or hyperactivity-impulsivity inappropriate to the patient's age which interfere with functioning in two or more settings (*e.g.*, school and home). Symptoms of inattention may include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity-impulsiveness may 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 both types of symptoms. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How Does Dexmethylphenidate Hydrochloride Work?

Dexmethylphenidate Hydrochloride is rapidly absorbed into the bloodstream and acts for a period of several hours. Dexmethylphenidate Hydrochloride helps to increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Before Dexmethylphenidate Hydrochloride 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 Dexmethylphenidate Hydrochloride 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 Dexmethylphenidate Hydrochloride 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.

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 Dexmethylphenidate Hydrochloride 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.

Who Should Not Take Dexmethylphenidate Hydrochloride?

You should NOT take Dexmethylphenidate Hydrochloride if:

- You have significant anxiety, tension, or agitation since Dexmethylphenidate Hydrochloride may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in Dexmethylphenidate Hydrochloride .
- 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.

How Should I Take Dexmethylphenidate Hydrochloride?

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.

What are the Possible Side Effects of Dexmethylphenidate Hydrochloride?

In the clinical studies with patients using Dexmethylphenidate Hydrochloride, the most common side effects were stomach pain, fever, decreased appetite, and nausea. Other side effects seen with Dexmethylphenidate Hydrochloride, include vomiting, dizziness, sleeplessness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

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.

What Must I Discuss with my Doctor before Taking Dexmethylphenidate Hydrochloride?

Talk to your doctor *before* taking Dexmethylphenidate Hydrochloride 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 Dexmethylphenidate Hydrochloride.

Can I Take Dexmethylphenidate Hydrochloride with Other Medicines?

Tell your doctor about *all* medicines that you are taking. Your doctor should decide whether you can take Dexmethylphenidate Hydrochloride with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take Dexmethylphenidate Hydrochloride with monoamine oxidase (MAO) inhibitors.

While on Dexmethylphenidate Hydrochloride, do not start taking a new medicine or herbal remedy before checking with your doctor.

Dexmethylphenidate Hydrochloride 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 Dexmethylphenidate Hydrochloride .

Other Important Safety Information

Abuse of Dexmethylphenidate Hydrochloride 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.

Before taking Dexmethylphenidate Hydrochloride, tell your doctor if you are pregnant or plan on becoming pregnant. If you take Dexmethylphenidate Hydrochloride, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking Dexmethylphenidate Hydrochloride .

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 gaining weight as your doctor expects, your doctor may stop your Dexmethylphenidate Hydrochloride treatment.

Call your doctor **immediately** if you take more than the amount of Dexmethylphenidate Hydrochloride prescribed by your doctor.

What Else Should I Know about Dexmethylphenidate Hydrochloride?

Dexmethylphenidate Hydrochloride has not been studied in children under 6 years of age.

Dexmethylphenidate Hydrochloride 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 Dexmethylphenidate Hydrochloride with anyone else and take only the number of Dexmethylphenidate Hydrochloride tablets prescribed by your doctor.

Dexmethylphenidate Hydrochloride may be taken at the same time as food or with no food. Dexmethylphenidate Hydrochloride should be stored in a safe place at room temperature (between 59° - 86° F). Do not store this medicine in hot, damp, or humid places.

Keep the container of Dexmethylphenidate Hydrochloride 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 number of tablets so that you will know if any are missing. Sadly, someone who has easy access to Dexmethylphenidate Hydrochloride may be able to give the tablets to others or misuse the medication.

Keep Out of the Reach of Children