HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DEXMETHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for DEXMETHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES.

DEXMETHYLPHENIDATE HYDROCHLORIDE extended-release Capsules, for oral use. CII

Initial U.S. Approval: 2005

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning

Dexmethylphenidate hydrochloride extended-release 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.

INDICATIONS AND USAGE

Dexmethylphenidate hydrochloride extended-release is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older (**1**)

DOSAGE AND ADMINISTRATION

- Dexmethylphenidate hydrochloride extended-release is intended for oral administration once daily in the morning. Dexmethylphenidate hydrochloride extended-release capsules may be swallowed whole, or capsule contents can be sprinkled on applesauce. Dexmethylphenidate hydrochloride extended-release and/or their contents should not be crushed, chewed, or divided (**2**)
- For patients new to methylphenidate: Begin treatment with dexmethylphenidate hydrochloride extended-release at 5 mg/day for pediatrics and 10 mg/day for adults, titrating the dose weekly in 5 mg increments for pediatrics and in 10 mg increments for adults. Doses above 30 mg/day in children and 40 mg/day in adults have not been studied. (**2.1**)
- For patients already using methylphenidate: Initiate dexmethylphenidate hydrochloride extended-release therapy with half (1/2) the current total daily dose of methylphenidate. (**2.2**)
- Patients already using dexmethylphenidate hydrochloride immediate release: switch to the same daily dose of dexmethylphenidate hydrochloride extended-release. (**2.2**)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg

CONTRAINDICATIONS

- Agitation, marked anxiety, and tension (**4.1**)
- Known hypersensitivity to methylphenidate or product components (**4.2**)
- Glaucoma (**4.3**)
- History of motor tics or a family history or diagnosis of Tourette's syndrome (**4.4**)
- During, or within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI) (**4.5**)

WARNINGS AND PRECAUTIONS

- Serious Cardiovascular Events: 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. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (**5.1**)
- Increased Blood Pressure and Heart Rate: have been reported. Monitor patients for changes in blood pressure and heart rate. Caution should be exercised in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate (**5.2**)
- Assess Cardiovascular Status: prior to stimulant treatment, assess for cardiac disease with history and exam and, if suggested by findings, conduct further cardiac evaluation. Patients with emerging symptoms suggestive of cardiac disease should undergo a prompt cardiac evaluation (**5.3**)
- Psychotic Symptoms: may be exacerbated in patients with psychotic disorders (**5.4**)
- Bipolar Disorder: Use with particular care in ADHD patients with comorbid Bipolar Disorder. Before initiating stimulant therapy, obtain a detailed psychiatric history for patients with comorbid depressive symptoms, in order to determine risk for Bipolar Disorder. (**5.5**)
- Emergence of New Psychotic or Manic Symptoms: Treatment-emergent psychotic or manic symptoms without a prior history can be caused by stimulants at usual doses. Discontinuation of stimulant therapy may be indicated (**5.6**)
- Aggression: Monitor for appearance of or worsening of aggressive behavior or hostility (**5.7**)
- Long-Term Suppression of Growth: monitor height and weight in pediatric patients at appropriate intervals. Patients who are not growing or gaining weight as expected may need to have their treatment interrupted (**5.8**)
- Seizures: The threshold for seizures may be lowered. In the presence of seizure, discontinue treatment. (**5.9**)
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed (**5.10**)
- Peripheral Vasculopathy, including Raynaud's phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (**5.11**)
- Visual Disturbance: difficulties with accommodation and blurring of vision have been reported with stimulant treatment (**5.12**)
- Hematologic Monitoring: periodic monitoring of CBC with differential is advised during prolonged therapy (**5.14**)

ADVERSE REACTIONS

Most common adverse reactions (at least 5% and twice the incidence among placebo-treated patients) are dyspepsia, decreased appetite, headache, and anxiety for pediatric patients and dry mouth, dyspepsia, headache, and anxiety for adult patients (**6**).

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Dexmethylphenidate hydrochloride extended-release should not be used in patients being treated (currently or within the preceding two weeks) with MAO Inhibitors (**4.5**)
- Dexmethylphenidate hydrochloride extended-release should be used cautiously with pressor agents (**7**)
- Antacids or acid suppressants could alter the release of dexmethylphenidate hydrochloride extended-release (**7**)
- Racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants, and tricyclic drugs (**7**)

USE IN SPECIFIC POPULATIONS

- Dexmethylphenidate hydrochloride extended-release should not be used in **children under 6 years of age** (**5.13**)
- Pregnancy: Limited human data. Based on animal data, may cause fetal harm (**8.1**).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (**8.3**).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: DRUG DEPENDENCE

Dexmethylphenidate hydrochloride extended-release 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 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.

1 INDICATIONS AND USAGE

Dexmethylphenidate hydrochloride extended-release is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older. The effectiveness of dexmethylphenidate hydrochloride extended-release in the treatment of ADHD in patients aged 6 years and older was established in two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD [see **CLINICAL STUDIES (14)**].

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused 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 Types 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 extended-release 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 children with this syndrome. Stimulants are not intended for use in the child 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 child's symptoms.

Long-Term Use

The effectiveness of dexmethylphenidate hydrochloride extended-release for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use dexmethylphenidate hydrochloride extended-release for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient [see **Dosage and Administration (2.3)**].

2 DOSAGE AND ADMINISTRATION

Dexmethylphenidate hydrochloride extended-release is for oral administration once daily in the morning.

Dexmethylphenidate hydrochloride extended-release may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Dexmethylphenidate hydrochloride extended-release and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

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

2.1 Patients New to Methylphenidate

The recommended starting dose of dexmethylphenidate hydrochloride extended-release for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day for pediatric patients and 10 mg/day for adult patients.

Dosage may be adjusted in 5 mg increments for pediatric patients and in 10 mg increments for adult patients. In general, dosage adjustments may proceed at approximately weekly intervals. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered. In dose-response (fixed-dose) studies (pediatric from 10 to 30 mg/day and adult from 20 to 40 mg/day), all doses were effective vs. placebo. There was no clear finding, however, of greater average benefits for the higher doses compared to the lower doses. Adverse events and discontinuations, however, were dose-related. Doses above 30 mg/day in pediatrics and 40 mg/day in adults have not been studied and are not recommended.

2.2 Patients Currently Using Methylphenidate

For patients currently using methylphenidate, the recommended starting dose of dexmethylphenidate hydrochloride extended-release is half the total daily dose of racemic methylphenidate. Patients currently using dexmethylphenidate hydrochloride may be switched to the same daily dose of dexmethylphenidate hydrochloride extended-release.

2.3 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 extended-release. 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 extended-release for extended periods in patients with ADHD should periodically reevaluate 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.

2.4 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.

3 DOSAGE FORMS AND STRENGTHS

5 mg, extended-release capsule, light blue opaque body and light blue opaque capsule, imprinted with black ink "par" on capsule and 048 on body.

10 mg, extended-release capsule, beige opaque body and beige opaque capsule, imprinted with black ink "par" on capsule and 049 on body.

15 mg, extended-release capsule, spring green opaque body and spring green opaque capsule, imprinted with black ink "par" on capsule and 090 on body.

20 mg, extended-release capsule, white opaque body and white opaque capsule, imprinted with black ink "par" on capsule and 248 on body.

25 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted with black ink "par" on capsule and 333 on body.

30 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted with black ink "par" on capsule and 539 on body.

35 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted with black ink "par" on capsule and 339 on body.

40 mg extended-release capsule, white opaque body and yellow transparent capsule, imprinted with black ink "par" on capsule and 546 on body.

4 CONTRAINDICATIONS

4.1 Agitation

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

4.2 Hypersensitivity to Methylphenidate

Dexmethylphenidate hydrochloride extended-release is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of the product. Hypersensitivity reactions, including angioedema and anaphylactic reactions, have been observed in patients treated with methylphenidate [see **Adverse Reactions (6.5**, **6.6)**].

4.3 Glaucoma

Dexmethylphenidate hydrochloride extended-release is contraindicated in patients with glaucoma.

4.4 Tics

Dexmethylphenidate hydrochloride extended-release is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome [see **Adverse Reactions (6.1)**].

4.5 Monoamine Oxidase Inhibitors

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

5 WARNINGS AND PRECAUTIONS

5.1 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 death, 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.

5.2 Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mmHg) and average heart rate (about 3 to 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.

5.3 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.

5.4 Pre-Existing Psychosis

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

5.5 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.

5.6 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 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

5.7 Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post marketing 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.

5.8 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. In the 7-week double-blind placebo-controlled study of dexmethylphenidate hydrochloride extended-release, the mean weight gain was greater for patients receiving placebo (+0.4 kg) than for patients receiving dexmethylphenidate hydrochloride extended-release (-0.5 kg). 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.

5.9 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.

5.10 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.11 Peripheral Vasculopathy, including Raynaud's phenomenon

Stimulants, including dexmethylphenidate hydrochloride extended-release, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treating with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.12 Visual Disturbance

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

5.13 Use in Children Under Six Years of Age

Dexmethylphenidate hydrochloride extended-release should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

5.14 Hematologic Monitoring

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

6 ADVERSE REACTIONS

Dexmethylphenidate hydrochloride extended-release was administered to 46 children and 7 adolescents with ADHD for up to 7 weeks and 206 adults with ADHD in clinical studies. During the clinical studies, 101 adult patients were treated for at least 6 months.

Adverse events during exposure were obtained primarily 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 listings that follow, MedDRA 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.

6.1 Adverse Events Associated with Discontinuation of Treatment in Acute Clinical Studies with Dexmethylphenidate Hydrochloride Extended-Release-Children

Overall, 50 of 684 children treated with dexmethylphenidate hydrochloride immediate-release formulation (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). None of the 53 dexmethylphenidate hydrochloride extended-release-treated pediatric patients discontinued treatment due to adverse events in the 7-week placebo-controlled study.

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

Table 1 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible dexmethylphenidate hydrochloride extended-release doses of 5 to 30 mg/day. The table includes only those events that occurred in 5% or more of patients treated with dexmethylphenidate hydrochloride extended-release and for which the incidence in patients treated with dexmethylphenidate hydrochloride extended-release 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 Events[1] Occurring During Double-Blind Treatment–Pediatric Patients

	Dexmethylphenidate Hydrochloride ER N=53	Placebo N=47
No. of Patients with AE's Total **Primary System Organ Class/ Adverse Event Preferred Term**	76%	57%
Gastrointestinal Disorders	38%	19%
Dyspepsia	8%	4%
Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

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

Table 2 below enumerates the incidence of dose-related adverse events that occurred during a fixed-dose, double-blind, placebo controlled trial of dexmethylphenidate hydrochloride extended-release up to 30 mg/day versus placebo in children and adolescents with ADHD.

Table 2: Dose-related Adverse Events from a Fixed-dose Study of Double-Blind Treatment in Pediatric Patients By Organ-System and Preferred Term

ADVERSE EVENT	Dexmethylphenidate Hydrochloride ER 10 mg/d N=64	Dexmethylphenidate Hydrochloride ER 20 mg/d N=60	Dexmethylphenidate Hydrochloride ER 30 mg/d N=58	Placebo N=63
Gastrointestinal Disorders	22%	23%	29%	24%
Vomiting	2%	8%	9%	0
Metabolism and Nutritional Disorders	16%	17%	22%	5%
Anorexia	5%	5%	7%	0
Psychiatric Disorders	19%	20%	38%	8%
Insomnia	5%	8%	17%	3%
Depression	0	0	3%	0
Mood swings	0	0	3%	2%
Other Adverse Events				
Irritability	0	2%	5%	0
Nasal Congestion	0	0	5%	0
Pruritus	0	0	3%	0

6.3 Adverse Events Associated with Discontinuation of Treatment in Clinical Studies with Dexmethylphenidate Hydrochloride Extended-Release-Adults

In the adult placebo-controlled study, 10.7% of the dexmethylphenidate hydrochloride extended-release-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among dexmethylphenidate hydrochloride extended-release-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

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

Table 3 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed dexmethylphenidate hydrochloride extended-release doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a dexmethylphenidate hydrochloride extended-release dose group and for which the incidences in patients treated with dexmethylphenidate hydrochloride extended-release appeared to increase with dose. 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 3. Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment–Adults

	Dexmethylphenidate Hydrochloride Extended-release 20 mg N=57	Dexmethylphenidate Hydrochloride Extended-release 30 mg N=54	Dexmethylphenidate Hydrochloride Extended-release 40 mg N=54	Placebo N=53
No. of Patients with AE's Total **Primary System Organ Class/ Adverse Event Preferred Term**	84%	94%	85%	68%
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1] Events, regardless of causality, for which the incidence was at least 5% in a Dexmethylphenidate Hydrochloride Extended-release group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with dexmethylphenidate hydrochloride extended-release at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 4 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of dexmethylphenidate hydrochloride extended-release in the treatment of ADHD.

Table 4. Changes (Mean ±SD) in Vital Signs and Weight by Randomized Dose during Double-Blind Treatment-Adults

	Dexmethylphenidate Hydrochloride ER 20 mg (N=57)	Dexmethylphenidate Hydrochloride ER 30 mg (N=54)	Dexmethylphenidate Hydrochloride ER 40 mg (N=54)	Placebo (N=53)
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

6.5 Post-Marketing Experience

The following additional adverse reactions have been identified during postapproval use of dexmethylphenidate hydrochloride extended release. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

Musculoskeletal: rhabdomyolysis

Immune System Disorders: hypersensitivity reactions, including angioedema and anaphylaxis

6.6 Adverse Events with Other Methylphenidate HCl Dosage Forms

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, tachycardia

Gastrointestinal: abdominal pain, nausea

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

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

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, aggressive behavior, libido changes

Skin/Subcutaneous: scalp hair loss

Urogenital: priapism

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.

7 DRUG INTERACTIONS

Dexmethylphenidate hydrochloride extended-release should not be used in patients being treated (currently or within the preceding two weeks) with MAO Inhibitors [see **Contraindications (4.5)**].

Because of possible effects on blood pressure, dexmethylphenidate hydrochloride extended-release should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Dexmethylphenidate hydrochloride is metabolized primarily to *d*-ritalinic acid by de-esterification and not through oxidative pathways.

The effects of gastrointestinal pH alterations on the absorption of dexmethylphenidate from dexmethylphenidate hydrochloride extended-release have not been studied. Since the modified release characteristics of dexmethylphenidate hydrochloride extended-release are pH dependent, the coadministration of antacids or acid suppressants could alter the release of dexmethylphenidate.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). 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 methylphenidate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C:

There are no adequate and well controlled studies of dexmethylphenidate hydrochloride in pregnant women. Dexmethylphenidate did not cause major malformations in rats or rabbits; however, it did cause delayed skeletal ossification and decreased post-weaning weight gain in rats. Dexmethylphenidate hydrochloride extended-release should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 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.

8.2 Labor and Delivery

Dexmethylphenidate hydrochloride extended-release has not been studied in labor and delivery.

8.3 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 extended-release is administered to a nursing woman. Information from 4 published case reports on the use of racemic methylphenidate during breastfeeding suggest that at

maternal doses of 35 to 80 mg/day, milk concentrations of methylphenidate range from undetectable to 15.4 ng/mL. Based on these limited data, the calculated infant daily dose for an exclusively breastfed infant would be about 0.4 to 2.9 mcg/kg/day or about 0.2 to 0.7% of the maternal weight adjusted dose.

8.4 Pediatric Use
The safety and efficacy of dexmethylphenidate hydrochloride extended-release in children under 6 years old have not been established. Long-term effects of dexmethylphenidate in children have not been well established (see **Warnings and Precautions (5.11)**).

In a study conducted in young rats, racemic methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13 to 14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of racemic methylphenidate on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the racemic MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use
Dexmethylphenidate hydrochloride extended-release has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class
Dexmethylphenidate hydrochloride extended-release, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

9.2 Abuse, Dependence, Tolerance
See complete boxed warning for drug abuse and dependence information at the beginning of **FULL PRESCRIBING INFORMATION**.

10 OVERDOSAGE

10.1 Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, 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.

Rhabdomyolysis has also been reported in overdose.

10.2 Poison Control Center
The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

10.3 Recommended Treatment
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from dexmethylphenidate hydrochloride extended-release.

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.

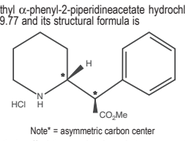
Efficacy of peritoneal dialysis for dexmethylphenidate overdosage has not been established.

11 DESCRIPTION

Dexmethylphenidate hydrochloride extended-release is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Each bead-filled dexmethylphenidate hydrochloride extended-release capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Dexmethylphenidate hydrochloride extended-release is available as a 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg extended-release capsule. Dexmethylphenidate hydrochloride extended-release 5, 10, 15, 20, 25, 30, 35 and 40 mg capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, 7.5, 10, 12.5, 15, 17.5 or 20 mg of dexmethylphenidate hydrochloride given b.i.d. as tablets.

Dexmethylphenidate hydrochloride, the *d-threo* enantiomer of racemic methylphenidate hydrochloride, is a central nervous system (CNS) stimulant.

Dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its molecular weight is 269.77 and its structural formula is



Note* = asymmetric carbon center

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.

Inactive ingredients methacrylic acid copolymer, amino methacrylate copolymer, triethyl citrate, talc, sugar spheres, polyethylene glycol, gelatin titanium dioxide and black ink. The black ink contains shellac glaze, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #1, FD&C Blue #2, FD&C Red#40 and D&C Yellow#10. The 5 mg also contains FD& C Blue #1 and FD&C Red #3. The 10 mg contains FD&C Yellow #6. The 15 mg contains FD&C Blue #1and FD&C Yellow #6. The 25 mg, 30 mg, 35 mg and 40 mg contains yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Dexmethylphenidate hydrochloride, the active ingredient in dexmethylphenidate hydrochloride extended-release, is a central nervous system stimulant. Dexmethylphenidate, the more pharmacologically active *d*-enantiomer of racemic 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. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

12.2 Pharmacodynamics
Effects on QT Interval
The effect of dexmethylphenidate hydrochloride extended-release on the QT interval was evaluated in a double-blind, placebo- and open label active (moxifloxacin)-controlled study following single doses of dexmethylphenidate hydrochloride extended-release 40 mg in 75 healthy volunteers. ECGs were collected up to 12 h post-dose. Frederica's method for heart rate correction was employed to derive the corrected QT interval (QTcF). The maximum mean prolongation of QTcF intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and there was no evident-exposure response relationship.

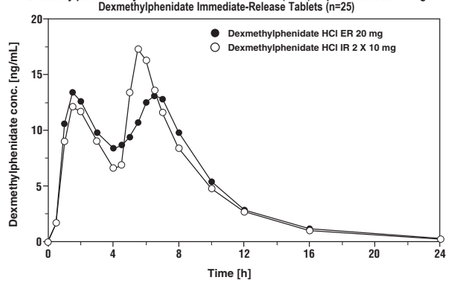
12.3 Pharmacokinetics
Absorption
Dexmethylphenidate hydrochloride extended-release produces a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately 4 hours apart) when orally administered to healthy adults. The initial rate of absorption for dexmethylphenidate hydrochloride extended-release is similar to that of dexmethylphenidate tablets as shown by the similar rate parameters between the two formulations, i.e., first peak concentration (C_{max1}), and time to the first peak (t_{max1}), which is reached in 1 ½ hours (typical range 1 to 4 hours). The mean time to the interpeak minimum (t_{minip}) is slightly shorter, and time to the second peak (t_{max2}) is slightly longer for dexmethylphenidate hydrochloride extended-release given once daily (about 6.5 hours, range 4.5 to 7 hours) compared to dexmethylphenidate tablets given in two doses 4 hours apart (see **Figure 1**), although the ranges observed are greater for dexmethylphenidate hydrochloride extended-release.

Dexmethylphenidate hydrochloride extended-release given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than dexmethylphenidate tablets given in two doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads (see **Figure 1**).

The AUC (exposure) after administration of dexmethylphenidate hydrochloride extended-release given once daily is equivalent to the same total dose of dexmethylphenidate tablets given in two doses 4 hours apart. The variability in C_{max}, C_{min}, and AUC is similar between dexmethylphenidate hydrochloride extended-release and dexmethylphenidate IR with approximately a three-fold range in each.

Radiolabeled racemic methylphenidate is well absorbed after oral administration with approximately 90% of the radioactivity recovered in urine. However, due to first pass metabolism the mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22 to 25%.

Figure 1 Mean Dexmethylphenidate Plasma Concentration-Time Profiles After Administration of 1 x 20 mg Dexmethylphenidate Hydrochloride Extended-Release (n=24) Capsules and 2 x 10 mg Dexmethylphenidate Immediate-Release Tablets (n=25)



Dose Proportionality
Dose proportionality of dexmethylphenidate hydrochloride extended-release was evaluated in a randomized, single-dose, five-period, cross-over study with administration of single doses of 5, 10, 20, 30 and 40 mg to healthy adults. Results confirmed dose proportionality within this dose range.

Food Effects
Administration times relative to meals and meal composition may need to be individually titrated.

No food effect study was performed with dexmethylphenidate hydrochloride extended-release. However, the effect of food has been studied in adults with racemic methylphenidate in the same type of extended-release formulation. The findings of that study are considered applicable to dexmethylphenidate hydrochloride extended-release. After a high fat breakfast, there was a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined. There is no evidence of dose dumping in the presence or absence of food. There were no differences in the plasma concentration-time profile, when administered with applesauce, compared to administration in the fasting condition. The results are expected not to differ for dexmethylphenidate hydrochloride extended-release.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered [see **DOSAGE AND ADMINISTRATION (2)**].

Distribution
The plasma protein binding of dexmethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12 to 15%, independent of concentration. Dexmethylphenidate shows a volume of distribution of 2.65±1.11 L/kg. Plasma dexmethylphenidate concentrations decline monophasically following oral administration of dexmethylphenidate hydrochloride extended-release.

Metabolism and Excretion
In humans, dexmethylphenidate 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 no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of no levels of *l-threo*-methylphenidate being detectable after administration of up to 40 mg dexmethylphenidate in adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic (*d,l*-) methylphenidate was *d,l*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5% of an intravenous dose.

In vitro studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes at concentrations observed after therapeutic doses.

Intravenous dexmethylphenidate was eliminated with a mean clearance of 0.40±0.12 L/kg.h^1 corresponding to 0.56±0.18 L/min. The mean terminal elimination half-life of dexmethylphenidate was just over 3 hours in healthy adults and typically varied between 2 and 4.5 hours with an occasional subject exhibiting a terminal half-life between 5 and 7 hours. Children tend to have slightly shorter half-lives with means of 2 to 3 hours.

Special Populations

Gender
After administration of dexmethylphenidate hydrochloride extended-release the first peak, (C_{max1}), was on average 45% higher in women. The interpeak minimum and the second peak also tended to be slightly higher in women although the difference was not statistically significant, and these patterns remained even after weight normalization. Pharmacokinetic parameters for dexmethylphenidate after dexmethylphenidate immediate-release tablets were similar for boys and girls.

Race
There is insufficient experience with the use of dexmethylphenidate hydrochloride extended-release to detect ethnic variations in pharmacokinetics.

Age
The pharmacokinetics of dexmethylphenidate after dexmethylphenidate hydrochloride extended-release administration have not been studied in children less than 18 years of age. When a similar formulation of racemic methylphenidate was examined in 15 children between 10 and 12 years of age and 3 children with ADHD between 7 and 9 years of age, the time to the first peak was similar, although the time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After administration of the same dose to children and adults, concentrations in children were approximately twice the concentrations observed in adults. This higher exposure is almost completely due to smaller body size as no relevant age-related differences in dexmethylphenidate pharmacokinetic parameters (i.e., clearance and volume of distribution) are observed after normalization to dose and weight.

Renal Insufficiency
There is no experience with the use of dexmethylphenidate hydrochloride extended-release 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 racemic ritalinic acid which is pharmacologically inactive. Very little unchanged drug is excreted in the urine, thus renal insufficiency is expected to have little effect on the pharmacokinetics of dexmethylphenidate hydrochloride extended-release.

Hepatic Insufficiency
There is no experience with the use of dexmethylphenidate hydrochloride extended-release in patients with hepatic insufficiency [see **DRUG INTERACTIONS (7)**].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
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.

Mutagenesis
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 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.

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

14 CLINICAL STUDIES

The effectiveness of dexmethylphenidate hydrochloride extended-release in the treatment of ADHD was established in randomized, double-blind, placebo-controlled, parallel-group studies in children and adolescents and in adults who met Diagnostic and Statistical Manual 4th edition (DSMIV) criteria for ADHD [see **INDICATIONS AND USAGE (1)**].

14.1 Children and Adolescents
The effectiveness of dexmethylphenidate hydrochloride extended-release was established in a randomized, double-blind, placebo-controlled, parallel-group study in 103 pediatric patients (ages 6 to 12, n=86; ages 13 to 17, n=17) who met DSM-IV criteria for ADHD. Patients were randomized to receive either a flexible dose of dexmethylphenidate hydrochloride extended-release (5 to 30 mg/day) or placebo once daily for 7 weeks. During the first 5 weeks of treatment patients were titrated to their optimal dose and in the last 2 weeks of the study patients remained on their optimal dose without dose changes or interruption.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for Focalin XR– and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the DSM-IV total subscale score of the Conners ADHD/DSM-IV Scales for teachers (CADS-T).

There was a statistically significant treatment effect in favor of dexmethylphenidate hydrochloride extended-release. There were insufficient adolescents enrolled in this study to assess the efficacy for dexmethylphenidate hydrochloride extended-release in the adolescent population. However, pharmacokinetic considerations and evidence of effectiveness of immediate-release Focalin in adolescents support the effectiveness of dexmethylphenidate hydrochloride extended-release in this population.

In two additional studies in pediatric patients aged 6 to 12 years who received 20 mg dexmethylphenidate hydrochloride extended-release or placebo in a cross-over design, dexmethylphenidate hydrochloride extended-release was found to have a statistically significant treatment effect versus placebo on the Swanson, Kotkin, Agler, M-Flynn & Pelham (SKAMP) rating scale combined score at all time points after dosing in each study (0.5, 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours in one study and 1, 2, 4, 6, 8, 9, 10, 11 and 12 hours in the other study). A treatment effect was also observed 0.5 hours after administration of dexmethylphenidate hydrochloride extended-release 20 mg in an additional study of ADHD patients aged 6 to 12 years. The SKAMP is a reliable and validated scale that assesses specific classroom behaviors related to attention (e.g., getting started, sticking with activities, completing work, and stopping for transition) and deportment or behavior (e.g., remaining quiet, remaining seated, interacting with other students, and interacting with the teacher.) Each item is rated on a 7-point impairment scale, and an average rating per item is calculated for the subscales of Attention and Deportment.

14.2 Adults
The effectiveness of dexmethylphenidate hydrochloride extended-release was established in a randomized, double-blind, placebo-controlled, parallel-group study in 221 adult patients (ages 18 to 60) who met DSM-IV criteria for ADHD. Patients were randomized to receive either a fixed dose of dexmethylphenidate hydrochloride extended-release (20, 30, or 40 mg/day) or placebo once daily for 5 weeks. Patients randomized to dexmethylphenidate hydrochloride extended-release were initiated on a 10 mg/day starting dose and titrated in increments of 10 mg/week to the randomly assigned fixed dose. Patients were maintained on their fixed dose (20, 30 or 40 mg/day) for a minimum of 2 weeks.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for dexmethylphenidate hydrochloride extended-release– and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the investigator-administered DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS).

All three dexmethylphenidate hydrochloride extended-release doses were statistically significantly superior to placebo. There was no obvious increase in effectiveness with increasing dose.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

5 mg Extended Release Capsules (NDC 49884-048-01) light blue opaque body with a light blue opaque cap printed with "par" on capsule and 048 on body in black ink supplied in bottles of 100.

10 mg Extended Release Capsules (NDC 49884-049-01) beige opaque body with a beige opaque cap printed with "par" on capsule and 049 on body in black ink supplied in bottles of 100.

15 mg Extended Release Capsules (NDC 49884-090-01) spring green opaque body with a spring green opaque cap printed with "par" on capsule and 090 on body in black ink supplied in bottles of 100.

20 mg Extended Release Capsules (NDC 49884-248-01) white opaque body with a white opaque cap printed with "par" on capsule and 248 on body in black ink supplied in bottles of 100.

25 mg Extended Release Capsules (NDC 49884-333-01) white opaque body with a yellow transparent cap printed with "par" on capsule and 333 on body in black ink supplied in bottles of 100.

30 mg Extended Release Capsules (NDC 49884-539-01) white opaque body with a yellow transparent cap printed with "par" on capsule and 539 on body in black ink supplied in bottles of 100.

35 mg Extended Release Capsules (NDC 49884-339-01) white opaque body with a yellow transparent cap printed with "par" on capsule and 339 on body in black ink supplied in bottles of 100.

40 mg Extended-Release Capsules (NDC 49884-546-01) white opaque body with a yellow transparent cap printed with "par" on capsule and 546 on body in black ink supplied in bottles of 100.

Store dexmethylphenidate hydrochloride extended-release at 20° to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

INFORMATION FOR PATIENTS

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with dexmethylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for dexmethylphenidate hydrochloride extended-release. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Priapism
Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism *[see* **Warnings and Precautions (5.10)***]*

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]

- Instruct patients beginning treatment with dexmethylphenidate hydrochloride extended-release about the risk of peripheral vasculopathy, including Raynaud's Phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- **Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking dexmethylphenidate hydrochloride extended-release.**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

MEDICATION GUIDE

Dexmethylphenidate Hydrochloride Extended-Release Capsules CII

(DEX-meth-il-FEN-i-date)

Read the Medication Guide that comes with dexmethylphenidate hydrochloride extended-release before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with dexmethylphenidate hydrochloride extended-release.

What is the most important information I should know about dexmethylphenidate hydrochloride extended-release capsules?

The following have been reported with use of dexmethylphenidate hydrochloride and other stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting dexmethylphenidate hydrochloride extended-release.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with dexmethylphenidate hydrochloride extended-release.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking dexmethylphenidate hydrochloride extended-release capsules.

2. Mental (Psychiatric) problems:

All Patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers

- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking dexmethylphenidate hydrochloride extended-release capsules, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

3. Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red

- Tell your doctor if you have or your child has numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.
- **Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking dexmethylphenidate hydrochloride extended-release**

What Is Dexmethylphenidate Hydrochloride Extended-Release?

Dexmethylphenidate hydrochloride extended-release is a central nervous system stimulant prescription medicine. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD)**. Dexmethylphenidate hydrochloride extended-release may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Dexmethylphenidate hydrochloride extended-release should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Dexmethylphenidate hydrochloride extended-release is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep dexmethylphenidate hydrochloride extended-release in a safe place to prevent misuse and abuse. Selling or giving away dexmethylphenidate hydrochloride extended-release may harm others, and is against the law.

Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take dexmethylphenidate hydrochloride extended-release capsules?

Dexmethylphenidate hydrochloride extended-release capsules should not be taken if you or your child:

- are very anxious, tense, or agitated
- have an eye problem called glaucoma
- have tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard to control repeated movements or sounds.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- are allergic to anything in dexmethylphenidate hydrochloride extended-release. See the end of this Medication Guide for a complete list of ingredients. Dexmethylphenidate hydrochloride extended-release should not be used in children less than 6 years old because it has not been studied in this age group.

Dexmethylphenidate hydrochloride extended-release capsules may not be right for you or your child. Before starting dexmethylphenidate hydrochloride extended-release capsules tell your or your child's doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- seizures or have had an abnormal brain wave test (EEG) Tell your doctor if you or your child is pregnant, planning to become pregnant, or breast-feeding.
- circulation problems in fingers or toes

Can dexmethylphenidate hydrochloride extended-release capsules be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. Dexmethylphenidate hydrochloride extended-release and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking dexmethylphenidate hydrochloride extended-release.

Your doctor will decide whether dexmethylphenidate hydrochloride extended-release can be taken with other medicines.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- antacids
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking dexmethylphenidate hydrochloride extended-release capsules without talking to your doctor first.

How should dexmethylphenidate hydrochloride extended-release capsules be taken?

- **Take dexmethylphenidate hydrochloride extended-release exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Take dexmethylphenidate hydrochloride extended-release once each day in the morning. Dexmethylphenidate hydrochloride extended-release is an extended-release capsule. It releases medicine into your body throughout the day.
- Dexmethylphenidate hydrochloride extended-release can be taken with or without food. Taking dexmethylphenidate hydrochloride extended-release with food may slow the time it takes for the medicine to start working.
- Swallow dexmethylphenidate hydrochloride extended-release capsules whole with water or other liquids. **Do not chew, crush, or divide the capsules or the beads in the capsule.** If you or your child cannot swallow the capsule, open it and sprinkle the small beads of medicine over a spoonful of applesauce and swallow it right away without chewing.
- From time to time, your doctor may stop dexmethylphenidate hydrochloride extended-release treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking dexmethylphenidate hydrochloride extended-release. Children should have their height and weight checked often while taking dexmethylphenidate hydrochloride extended-release. Dexmethylphenidate hydrochloride extended-release treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much dexmethylphenidate hydrochloride extended-release or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of dexmethylphenidate hydrochloride extended-release capsules?

See **"What is the most important information I should know about dexmethylphenidate hydrochloride extended-release?"** for information on reported heart and mental problems.

Other serious side effects include:

- serious allergic reactions (symptoms can be difficulty breathing, swelling of the face, neck and throat, rashes and hives, fever)
- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- painful and prolonged erections (priapism) have occurred with methylphenidate. If you or your child develop priapism seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- eyesight changes or blurred vision

Common side effects include:

- headache
- decreased appetite
- upset stomach
- dry mouth
- dizziness
- trouble sleeping
- nervousness
- anxiety

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

How should I store dexmethylphenidate hydrochloride extended-release capsules?

- Store dexmethylphenidate hydrochloride extended-release in a safe place at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
- **Keep dexmethylphenidate hydrochloride extended-release and all medicines out of the reach of children.**

General information about dexmethylphenidate hydrochloride extended-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use dexmethylphenidate hydrochloride extended-release for a condition for which it was not prescribed. Do not give dexmethylphenidate hydrochloride extended-release to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about dexmethylphenidate hydrochloride extended-release. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about dexmethylphenidate hydrochloride extended-release that was written for healthcare professionals. For more information about dexmethylphenidate hydrochloride extended-release call 1-800-828-9393.

What are the ingredients in dexmethylphenidate hydrochloride extended-release capsules?

Active Ingredient: dexmethylphenidate hydrochloride

Inactive Ingredients: methacrylic acid copolymer, amino methacrylate copolymer, triethyl citrate, talc, sugar spheres, polyethylene glycol, gelatin titanium dioxide and black ink. The black ink contains shellac glaze, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #1, FD&C Blue #2, FD&C Red#40 and D&C Yellow#10. The 5 mg also contains FD& C Blue #1 and FD&C Red #3. The 10 mg contains FD&C Yellow #6. The 15 mg contains FD&C Blue #1and FD&C Yellow #6. The 25 mg, 30 mg, 35 mg and 40 mg contains yellow iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
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Chestnut Ridge, NY 10977

Revised: 01/16 OS048-01-1-04