DEXMETHYLPHENIDATE HYDROCHLORIDE extended-release capsules, CII

5221450

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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: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3).**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2).**

--- INDICATIONS AND USAGE ---

Dexmethylphenidate hydrochloride extended-release capsules are a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (1).

--- DOSAGE AND ADMINISTRATION ---

- Patients new to methylphenidate: Recommended starting dose is 5 mg once daily for pediatric patients and 10 mg once daily for adults with or without food in the morning (2.2).
- Patients currently on methylphenidate: Dexmethylphenidate hydrochloride extended-release capsules dosage is half (1/2) the current total daily dosage of methylphenidate (2.2).
- Patients currently on dexmethylphenidate hydrochloride immediate-release tablets: Give the same daily dose of dexmethylphenidate hydrochloride extended-release capsules (2.2).
- Titrate weekly in increments of 5 mg in pediatric patients and 10 mg in adult patients (2.2).
- Maximum recommended daily dose: 30 mg in pediatric patients and 40 mg in adults (2.2).
- Capsules may be swallowed whole or opened and the entire contents sprinkled on applesauce (2.3).

--- DOSAGE FORMS AND STRENGTHS ---

Extended-Release Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg of dexmethylphenidate hydrochloride (3).

--- CONTRAINDICATIONS ---

- Known hypersensitivity to methylphenidate or other components of dexmethylphenidate hydrochloride extended-release capsules (4).
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4).

--- WARNINGS AND PRECAUTIONS ---

- *Serious Cardiovascular Events:* Sudden death has been reported in association with CNS stimulant treatment at usual doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm arrhythmias, or coronary artery disease (5.2).
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risk in patients for whom an increase in blood pressure or heart rate would be problematic (5.3).
- *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychiatric illness. Evaluate for existing psychotic or bipolar disorder prior to dexmethylphenidate hydrochloride extended-release capsules use (5.4).
- *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 (5.5).
- *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 (5.6).
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients (5.7).

--- ADVERSE REACTIONS ---

The most common adverse reactions (greater than or equal to 5% and twice the rate of placebo):

- Pediatric patients 6 to 17 years: dyspepsia, decreased appetite, headache, and anxiety (6.1).
- Adults: dry mouth, dyspepsia, headache, pharyngolaryngeal pain, and anxiety (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---

- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed (7.1).
- Halogenated Anesthetics: Avoid use of dexmethylphenidate hydrochloride extended-release capsules on the day of surgery if halogenated anesthetics will be used (7.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Warnings and Precautions (5.1)*, Drug *Abuse and Dependence (9.2, 9.3)*].

1 INDICATIONS AND USAGE

Dexmethylphenidate hydrochloride extended-release capsules are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) *[see Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating pediatric patients and adults with central nervous system (CNS) stimulants, including dexmethylphenidate hydrochloride extended-release capsules, assess for the presence of cardiac disease (i.e., perform a careful history, including family history of sudden death or ventricular arrhythmia, and physical examination) [*see Warnings and Precautions (5.2)*].

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically reevaluate the need for dexmethylphenidate hydrochloride extended-release capsules use [*see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].*

2.2 Treatment of Attention Deficit Hyperactivity Disorder

Patients New to Methylphenidate

The recommended starting dosage of dexmethylphenidate hydrochloride extended-release capsules for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate are:

- Pediatric patients: Start with 5 mg orally once daily in the morning with or without food.
- Adult patients: Start with 10 mg orally once daily in the morning with or without food.

Patients Currently on Methylphenidate

The recommended starting dose of dexmethylphenidate hydrochloride extended-release capsules for patients currently using methylphenidate is half (1/2) the total daily dose of racemic methylphenidate.

Patients currently using dexmethylphenidate hydrochloride immediate-release tablets may be given the same daily dose of dexmethylphenidate hydrochloride extended-release capsules.

Titration Schedule

The dose may be titrated weekly in increments of 5 mg in pediatric patients and 10 mg in adult patients. The dose should be individualized according to the needs and response of the patient. Daily doses above 30 mg in pediatrics and 40 mg in adults have not been studied and are not recommended.

Maintenance/Extended Treatment

Pharmacological treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of dexmethylphenidate hydrochloride extended-release capsules and adjust dosage as needed.

2.3 Administration Instructions

Dexmethylphenidate hydrochloride extended-release capsules are administered orally and may be taken whole or the capsule may be opened and the entire contents sprinkled onto applesauce. If the patient is using the sprinkled administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

2.4 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur, reduce the dosage, or if necessary, discontinue dexmethylphenidate hydrochloride extended-release capsules. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg Extended-Release Capsules: powder blue colored cap and body imprinted with '621' on cap and '5 mg' on body in black ink containing white to off-white pellets.
- 10 mg Extended-Release Capsules: yellow colored cap and body imprinted with '622' on cap and '10 mg' on body in black ink containing white to off-white pellets.
- 15 mg Extended-Release Capsules: turquoise colored cap and body imprinted with '623' on cap and '15 mg' on body in black ink containing white to off-white pellets.
- 20 mg Extended-Release Capsules: white colored cap and body imprinted with '624' on cap and '20 mg' on body in black ink containing white to off-white pellets.
- 25 mg Extended-Release Capsules: powder blue colored cap and white colored body imprinted with '628' on cap and '25 mg' on body in black ink containing white to off-white pellets.
- 30 mg Extended-Release Capsules: yellow colored cap and white colored body imprinted with '625' on cap and '30 mg' on body in black ink containing white to off-white pellets.
- 35 mg Extended-Release Capsules: powder blue colored cap and yellow colored body imprinted with '629' on cap and '35 mg' on body in black ink containing white to off-white pellets.
- 40 mg Extended-Release Capsules: turquoise colored cap and white colored body imprinted with '626' on cap and '40 mg' on body in black ink containing white to off-white pellets.

4 CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or other components of dexmethylphenidate hydrochloride extended-release capsules. Hypersensitivity reactions, such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate [*see Adverse Reactions (6.1)*].
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crises [*see Drug Interactions (7.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS-stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during dexmethylphenidate hydrochloride extended-release capsules treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 beats per minute). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing dexmethylphenidate hydrochloride extended-release capsules. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 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.

5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon

CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, 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 treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

In a 7-week, double-blind, placebo-controlled study of dexmethylphenidate hydrochloride extended-release capsules, the mean weight gain was greater for pediatric patients (ages 6 to 17 years) receiving placebo (+0.4 kg) than for patients receiving dexmethylphenidate hydrochloride extended-release capsules (-0.5 kg).

Careful follow-up of weight and height in pediatric patients 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 patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (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.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Abuse and Dependence *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Known hypersensitivity to methylphenidate or other ingredients of dexmethylphenidate hydrochloride extended-release capsules *[see Contraindications (4)]*
- Hypertensive Crisis with Concomitant Use of Monoamine Oxidase Inhibitors *[see Contraindications (4), Drug Interactions (7.1)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, Including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Dexmethylphenidate Hydrochloride Extended-Release Capsules in Pediatric Patients with ADHD

The safety data in this section is based on data from a 7-week controlled clinical study of dexmethylphenidate hydrochloride extended-release capsules in 100 (103 randomized) pediatric patients with ADHD ages 6 to 17 years (ages 6 to 12, n = 86; ages 13 to 17, n = 17).

This study was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the time of onset, duration of efficacy, tolerability, safety of dexmethylphenidate hydrochloride extended-release capsules 5 mg to 30 mg/day who met The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD *[see Clinical Studies (14.1)].*

Most Common Adverse Reactions (incidence of greater than or equal to 5% and at least twice placebo): dyspepsia, decreased appetite, headache, and anxiety.

Adverse Reactions Leading to Discontinuation: 50 of 684 (7.3%) pediatric patients treated with dexmethylphenidate hydrochloride immediate-release tablets experienced an adverse reaction 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).

Table 1 enumerates adverse reactions for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible dexmethylphenidate hydrochloride extended-release capsules doses of 5–30 mg/day. The table includes only those events that occurred in 5% or more of patients treated with dexmethylphenidate hydrochloride extended-release capsules and for which the incidence in patients treated with dexmethylphenidate hydrochloride extended-release capsules was at least twice the incidence in placebo-treated patients.

Table 1: Common Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class Adverse Reaction	Dexmethylphenidate Hydrochloride Extended-Release Capsules N= 53	Placebo N= 47
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%

Abbreviation: ADHD, attention deficit hyperactivity disorder.

Table 2 below enumerates the incidence of dose-related adverse reactions that occurred during a fixed-dose, double-blind, placebo-controlled trial in pediatric patients with ADHD taking dexmethylphenidate hydrochloride extended-release capsules up to 30 mg daily versus placebo. The table includes only those reactions that occurred in patients treated with dexmethylphenidate hydrochloride extended-release capsules for which the incidence was at least 5% and greater than the incidence among placebo-treated patients.

Table 2: Dose-Related Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class Adverse Reaction	Dexmethylphenidate Hydrochloride Extended-Release Capsules 10 mg/day N = 64	Dexmethylphenidate Hydrochloride Extended-Release Capsules 20 mg/day N = 60	Dexmethylphenidate Hydrochloride Extended-Release Capsules 30 mg/day 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 Reactions				
Irritability	0%	2%	5%	0%
Nasal congestion	0%	0%	5%	0%
Pruritus	0%	0%	3%	0%

Abbreviation: ADHD, attention deficit hyperactivity disorder.

Clinical Trials Experience with Dexmethylphenidate Hydrochloride Extended-Release Capsules in Adult Patients with ADHD

The safety data in this section is based on data from a 5-week controlled clinical study of dexmethylphenidate hydrochloride extended-release capsules in 218 adult patients (221 randomized) with ADHD ages 18 to 60 years. In this study, 101 adult patients were treated for at least 6 months.

This study was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of dexmethylphenidate hydrochloride extended-release capsules 20 mg, 30 mg, or 40 mg daily who met DSM-IV criteria for ADHD *[see Clinical Studies (14.2)].*

Most Common Adverse Reactions (incidence of greater than or equal to 5% and at least twice placebo): dry mouth, dyspepsia, headache, anxiety, and pharyngolaryngeal pain.

Adverse Reactions Leading to Discontinuation: During the double-blind phase of the study, 10.7% of the dexmethylphenidate hydrochloride extended-release capsules-treated patients and 7.5% of the placebo-treated patients discontinued due to adverse reactions. Three patients (1.8%) in the dexmethylphenidate hydrochloride extended-release capsules discontinued due to insomnia and jittery, respectively and two patients (1.2%) in the dexmethylphenidate hydrochloride extended-release capsules discontinued due to anorexia and anxiety, respectively.

Table 3 enumerates adverse reactions for the placebo-controlled, parallel-group study in adults with ADHD at fixed dexmethylphenidate hydrochloride extended-release capsules 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 capsules dose group and for which the incidences in patients treated with dexmethylphenidate hydrochloride extended-release capsules appeared to increase with dose.

Table 3: Dose-Related Adverse Reactions in Adult Patients (18 to 60 years of age) with ADHD

System Organ Class Adverse Reaction	Dexmethylphenidate Hydrochloride Extended-Release Capsules 20 mg N=57	Dexmethylphenidate Hydrochloride Extended-Release Capsules 30 mg N=54	Dexmethylphenidate Hydrochloride Extended-Release Capsules 40 mg N=54	Placebo N=53
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%

Two other adverse reactions occurring in clinical trials with dexmethylphenidate hydrochloride extended-release capsules 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 capsules 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 Extended-Release Capsules 20 mg (N=57)	Dexmethylphenidate Hydrochloride Extended-Release Capsules 30 mg (N=54)	Dexmethylphenidate Hydrochloride Extended-Release Capsules 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

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of dexmethylphenidate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal: rhabdomyolysis

Immune System Disorders: hypersensitivity reactions, including angioedema and anaphylaxis

Adverse Reactions Reported with All Methylphenidate Hydrochloride and Dexmethylphenidate Hydrochloride Formulations

The following adverse reactions associated with the use of all methylphenidate hydrochloride and dexmethylphenidate hydrochloride formulations were identified in clinical trials, spontaneous reports, and literature. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Infections and Infestations: nasopharyngitis

Blood and the Lymphatic System Disorders: leukopenia, thrombocytopenia, anemia

Immune System Disorders: hypersensitivity reactions, including angioedema and anaphylaxis

Metabolism and Nutrition Disorders: decreased appetite, reduced weight gain, and suppression of growth during prolonged use in pediatric patients

Psychiatric Disorders: insomnia, anxiety, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), depressed mood

Nervous System Disorders: headache, dizziness, tremor, dyskinesia, including choreoathetoid movements, drowsiness, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents), serotonin syndrome in combination with serotonergic drugs

Eye Disorders: blurred vision, difficulties in visual accommodation

Cardiac Disorders: tachycardia, palpitations, increased blood pressure, arrhythmias, angina pectoris

Respiratory, Thoracic, and Mediastinal Disorders: cough

Gastrointestinal Disorders: dry mouth, nausea, vomiting, abdominal pain, dyspepsia

Hepatobiliary Disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus, urticaria, exfoliative dermatitis, scalp hair loss, erythema multiforme rash, thrombocytopenic purpura

Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle cramps, rhabdomyolysis

Investigations: weight loss (adult ADHD patients)

Additional Adverse Reactions Reported with Other Methylphenidate Products

The list below shows adverse reactions not listed with methylphenidate hydrochloride and dexmethylphenidate hydrochloride formulations that have been reported with other methylphenidate products based on clinical trials data and post-marketing spontaneous reports.

Blood and Lymphatic Disorders: pancytopenia

Immune System Disorders: hypersensitivity reactions, such as auricular swelling, bullous conditions, eruptions, exanthemas

Psychiatric Disorders: affect lability, mania, disorientation, libido changes

Nervous System Disorders: migraine

Eye Disorders: diplopia, mydriasis

Cardiac Disorders: sudden cardiac death, myocardial infarction, bradycardia, extrasystole, supraventricular tachycardia, ventricular extrasystole

Vascular Disorders: peripheral coldness, Raynaud's phenomenon

Respiratory, Thoracic, and Mediastinal Disorders: pharyngolaryngeal pain, dyspnea

Gastrointestinal Disorders: diarrhea, constipation

Skin and Subcutaneous Tissue Disorders: angioneurotic edema, erythema, fixed drug eruption

Musculoskeletal, Connective Tissue, and Bone Disorders: myalgia, muscle twitching

Renal and Urinary Disorders: hematuria

Reproductive System and Breast Disorders: gynecomastia

General Disorders: fatigue, hyperpyrexia

Urogenital Disorders: priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions with Dexmethylphenidate Hydrochloride Extended-Release Capsules

Table 5 presents clinically important drug interactions with dexmethylphenidate hydrochloride extended-release capsules.

Table 5: Clinically Important Drug Interactions with Dexmethylphenidate Hydrochloride Extended-Release Capsules

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.
Intervention	Concomitant use of dexmethylphenidate hydrochloride extended-release capsules with MAOIs or within 14 days after discontinuing MAOI treatment is contraindicated.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
Clinical Impact	Dexmethylphenidate hydrochloride extended-release capsules may decrease the effectiveness of drugs used to treat hypertension *[see Warnings and Precautions (5.3)]*.
Intervention	Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
Examples	Potassium-sparing and thiazide diuretics, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, centrally acting alpha-2 receptor agonists
Halogenated Anesthetics	
Clinical Impact	Concomitant use of halogenated anesthetics and dexmethylphenidate hydrochloride extended-release capsules may increase the risk of sudden blood pressure and heart rate increase during surgery.
Intervention	Avoid use of dexmethylphenidate hydrochloride extended-release capsules in patients being treated with anesthetics on the day of surgery.
Examples	halothane, isoflurane, enflurane, desflurane, sevoflurane
Risperidone	
Clinical Impact	Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS)
Intervention	Monitor for signs of EPS

MEDICATION GUIDE
Dexmethylphenidate Hydrochloride Extended-Release Capsules, CII
(dex-METH-il-FEN-i-date)

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

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

Tell your doctor if you or your child have abused or been dependent on alcohol, prescription medicines, or street drugs.

The following have been reported with use of methylphenidate 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 capsules.

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

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**
- **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.

What are dexmethylphenidate hydrochloride extended-release capsules?

- Dexmethylphenidate hydrochloride extended-release capsules are a central nervous system stimulant (CNS) prescription medicine. **They are used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).** Dexmethylphenidate hydrochloride extended-release capsules may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.
- Dexmethylphenidate hydrochloride extended-release capsules should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Who should not take dexmethylphenidate hydrochloride extended-release capsules:

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

- are allergic to methylphenidate hydrochloride, or any of the ingredients in dexmethylphenidate hydrochloride extended-release capsules. See the end of this Medication Guide for a complete list of ingredients in dexmethylphenidate hydrochloride extended-release capsules.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor (MAOI).

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
- circulation problems in fingers or toes
- if you are pregnant or plan to become pregnant. It is not known if dexmethylphenidate hydrochloride extended-release capsules will harm your unborn baby.
  - There is a pregnancy registry for females who are exposed to ADHD medications, including dexmethylphenidate hydrochloride extended-release capsules, during pregnancy. The purpose of the registry is to collect information about the health of females exposed to dexmethylphenidate hydrochloride extended-release capsules and their baby. If you or your child becomes pregnant during treatment with dexmethylphenidate hydrochloride extended-release capsules, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhd-medications/.
- if you are breastfeeding or plan to breastfeed. Dexmethylphenidate hydrochloride extended-release capsules pass into your breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with dexmethylphenidate hydrochloride extended-release capsules.

Tell your doctor about all of the medicines that you or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Dexmethylphenidate hydrochloride extended-release capsules 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 capsules.

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

Especially tell your doctor if you or your child takes:

- anti-depression medicines, including MAOIs
- blood pressure medicines (anti-hypertensive)

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

- You should not take dexmethylphenidate hydrochloride extended-release capsules on the day of your operation if a certain type of anesthetic is used. This is because there is a chance of a sudden rise in blood pressure and heart rate during the operation.

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 capsules exactly as prescribed. Your doctor may adjust the dose until it is right for you or your child.

- Take dexmethylphenidate hydrochloride extended-release capsules once each day in the morning. Dexmethylphenidate hydrochloride extended-release capsules are extended-release capsules.
- Dexmethylphenidate hydrochloride extended-release capsules can be taken with or without food. Taking dexmethylphenidate hydrochloride extended-release capsules 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 capsules 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 capsules.
- Children should have their height and weight checked often while taking dexmethylphenidate hydrochloride extended-release capsules. Dexmethylphenidate hydrochloride extended-release capsules treatment may be stopped if a problem is found during these check-ups.
- **In case of poisoning, call your poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.**

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

Dexmethylphenidate hydrochloride extended-release capsules may cause serious side effects, including:

- see **"What is the most important information I should know about dexmethylphenidate hydrochloride extended-release capsules?"** for information on reported heart and mental problems.
- **painful and prolonged erections (priapism)** have occurred with methylphenidate. If you or your child develops priapism, seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- **circulation problems in fingers and toes** (peripheral vasculopathy, including Raynaud's phenomenon):
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

Tell your doctor if you or your child have, numbness, pain, skin color change, or sensitivity to temperature in the 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 capsules.**
- **Slowing of growth (height and weight) in children**

Common side effects include:

Children (6–17 years)

- dyspepsia
- decreased appetite
- headache
- anxiety

Adults

- dry mouth
- dyspepsia
- headache
- anxiety
- pharyngolaryngeal pain

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

How should I store dexmethylphenidate hydrochloride extended-release capsules?

- Store dexmethylphenidate hydrochloride extended-release capsules in a safe place and in a tightly closed container at room temperature between 68°F to 77°F (20°C to 25°C).
- Dispose of remaining, unused, or expired dexmethylphenidate hydrochloride extended-release capsules by a medicine take-back program at authorized collection sites, such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix dexmethylphenidate hydrochloride extended-release capsules with an undesirable, nontoxic substance, such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container, such as a sealed plastic bag and throw away (discard) dexmethylphenidate hydrochloride extended-release capsules in the household trash.
- **Keep dexmethylphenidate hydrochloride extended-release capsules and all medicines out of the reach of children.**

General information about the safe and effective use of dexmethylphenidate hydrochloride extended-release capsules.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about dexmethylphenidate hydrochloride extended-release capsules that is written for healthcare professionals. Do not use dexmethylphenidate hydrochloride extended-release capsules for a condition for which it was not prescribed. Do not give dexmethylphenidate hydrochloride extended-release capsules to other people, even if they have the same symptoms that you have. It may harm them and it is against the law.

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

Active ingredient: dexmethylphenidate hydrochloride

Inactive ingredients: ammonio methacrylate copolymer (Type B), black iron oxide, D&C Red No. 28 (15 mg, and 40 mg strengths), FD&C Blue No. 1 (15 mg, and 40 mg strengths), FD&C Blue No. 2 (5 mg, 25 mg, and 35 mg strengths), gelatin, hypromellose, methacrylic acid and methyl methacrylate copolymer (1:1), methacrylic acid and methyl methacrylate copolymer (1:2), polyethylene glycol, propylene glycol, shellac, sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10 mg, 15 mg, 30 mg, 35 mg, and 40 mg strengths).

Manufactured by:
Ohm Laboratories Inc.
New Brunswick, NJ 08901

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

For more information, call 1-800-818-4555.

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

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including dexmethylphenidate hydrochloride extended-release capsules, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD medications at 1-866-961-2388 or visit https://womensmentalhealth.org/adhd-medications/.

Risk Summary

Dexmethylphenidate is the d-threo enantiomer of racemic methylphenidate. Published studies and postmarketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy (see Clinical Considerations). Embryo-fetal development studies in rats showed delayed fetal skeletal ossification at doses up to 5 times the maximum recommended human dose (MRHD) of 20 mg/day given to adults based on plasma levels. A decrease in pup weight in males was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 5 times the MRHD of 20 mg/day given to adults based on plasma levels (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulants, such as dexmethylphenidate hydrochloride extended-release capsules, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In embryo-fetal development 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 malformations 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, post-weaning 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 [area under the curves (AUCs)] of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with 20 mg/day. Plasma levels in adults were comparatively similar to plasma levels in adolescents.

Racemic methylphenidate has been shown to cause malformations (increased incidence of fetal spina bifida) in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

8.2 Lactation

Risk Summary

Dexmethylphenidate is the d-threo enantiomer of racemic methylphenidate. Limited published literature, based on milk sampling from seven mothers reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dexmethylphenidate hydrochloride extended-release capsule and any potential adverse effects on the breastfed infant from dexmethylphenidate hydrochloride extended-release capsule or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of dexmethylphenidate hydrochloride extended-release capsules in pediatric patients less than 6 years have not been established.

The safety and effectiveness of dexmethylphenidate hydrochloride extended-release capsules for the treatment of ADHD have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials *[see Clinical Studies (14.2)]*. The long-term efficacy of dexmethylphenidate hydrochloride extended-release capsules in pediatric patients has not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including dexmethylphenidate hydrochloride extended-release capsules. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

Juvenile Animal Toxicity Data

Rats treated with racemic methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the MRHD of 60 mg/day given to children on a mg/m^2 basis.

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 4 times the MRHD of 60 mg/day of racemic methylphenidate given to children 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 (8 times the MRHD given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.5 times the MRHD given to children 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 capsules have not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Dexmethylphenidate hydrochloride extended-release capsules contain dexmethylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is characterized by impaired control over drug use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which may result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants *[see How Supplied/Storage and Handling (16)]*, monitor for signs of abuse while on therapy, and reevaluate the need for dexmethylphenidate hydrochloride extended-release capsules use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules.

Dependence

Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

Human Experience

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

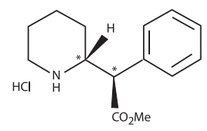
Overdose Management

Consult with a Certified Poison Control Center (1-800-222-1222) for the latest recommendations.

11 DESCRIPTION

Dexmethylphenidate hydrochloride extended-release capsules contain dexmethylphenidate hydrochloride, a CNS stimulant. Dexmethylphenidate hydrochloride is the *d- threo* enantiomer of racemic methylphenidate hydrochloride. Dexmethylphenidate hydrochloride extended-release capsules are 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 delayed release of dexmethylphenidate. Dexmethylphenidate hydrochloride extended-release capsules are intended for oral administration and are available as 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg extended-release capsules.

Chemically, dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its molecular formula is $C_{14}H_{19}NO_2$•HCl. 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. Its molecular weight is 269.77 g/mol.

Inactive ingredients: ammonio methacrylate copolymer (Type B), black iron oxide, D&C Red No. 28 (15 mg, and 40 mg strengths), FD&C Blue No. 1 (15 mg, and 40 mg strengths), FD&C Blue No. 2 (5 mg, 25 mg, and 35 mg strengths), gelatin, hypromellose, methacrylic acid and methyl methacrylate copolymer (1:1), methacrylic acid and methyl methacrylate copolymer (1:2), polyethylene glycol, propylene glycol, shellac, sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10 mg, 15 mg, 30 mg, 35 mg, and 40 mg strengths).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmethylphenidate hydrochloride is a CNS stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Dexmethylphenidate is the more pharmacologically active d-enantiomer of racemic methylphenidate. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Cardiac Electrophysiology

At the recommended maximum total daily dosage of 40 mg, dexmethylphenidate hydrochloride extended-release capsules do not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

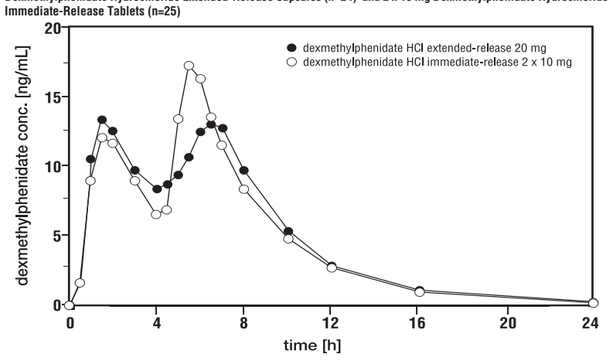
Dexmethylphenidate hydrochloride extended-release capsules produce a bi-modal plasma concentration-time profile (i.e., 2 distinct peaks approximately 4 hours apart) when orally administered to healthy adults. The initial rate of absorption for dexmethylphenidate hydrochloride extended-release capsules is similar to that of dexmethylphenidate hydrochloride immediate-release tablets as shown by the similar rate parameters between the 2 formulations, i.e., first peak concentration (C_{max1}), and time to the first peak (t_{max1}), which is reached in 1.5 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 capsules given once daily (about 6.5 hours; range, 4.5 to 7 hours) compared to dexmethylphenidate hydrochloride immediate-release tablets given in 2 doses 4 hours apart (see Figure 1), although the ranges observed are greater for dexmethylphenidate hydrochloride extended-release capsules.

Dexmethylphenidate hydrochloride extended-release capsules given once daily exhibit a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and fewer peak and trough fluctuations than dexmethylphenidate hydrochloride immediate-release tablets given in 2 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 ratio of geometric mean of $AUC_{(0\text{-}inf)}$ and C_{max} after administration of dexmethylphenidate hydrochloride extended-release capsules given once daily are 1.02 and 0.86 respectively, to the same total dose of dexmethylphenidate hydrochloride immediate-release tablets given in 2 doses 4 hours apart. The variability in C_{max}, C_{min}, and AUC is similar between dexmethylphenidate hydrochloride extended-release capsules and dexmethylphenidate hydrochloride immediate-release tablets with approximately a 3-fold range in each.

Approximately 90% of the dose is absorbed after oral administration of radiolabeled racemic methylphenidate. 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 1 x 20 mg Dexmethylphenidate Hydrochloride Extended-Release Capsules (n=24) and 2 x 10 mg Dexmethylphenidate Hydrochloride Immediate-Release Tablets (n=25)



After single dose administration, dexmethylphenidate hydrochloride extended-release capsules demonstrated dose proportional pharmacokinetics (PK) in the range of 5 mg to 40 mg.

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.

Elimination

Plasma dexmethylphenidate concentrations decline monophasically following oral administration of dexmethylphenidate hydrochloride extended-release capsules. The mean terminal elimination half-life of dexmethylphenidate was about 3 hours in healthy adults. Pediatric patients tend to have slightly shorter half-lives with means of 2 to 3 hours. Dexmethylphenidate was eliminated with a mean clearance of 0.40 ± 0.12 L/hr/kg after intravenous administration.

Metabolism

In humans, dexmethylphenidate is metabolized primarily via de-esterification to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid). This metabolite has little or no pharmacological activity. There is no *in vivo* interconversion to the *l-threo*-enantiomer.

Excretion

After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic *dl*- methylphenidate was *dl*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5% of an intravenous dose.

Studies in Specific Populations

Male and Female Patients

After administration of dexmethylphenidate hydrochloride extended-release capsules, 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.

Racial or Ethnic Groups

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

Pediatric Patients

The pharmacokinetics of dexmethylphenidate after dexmethylphenidate hydrochloride extended-release capsules administration have not been studied in pediatrics less than 18 years of age. When a similar formulation of racemic methylphenidate was examined in 15 patients between 10 and 12 years of age, and 3 patients 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 pediatric patients compared to adults. After administration of the same dose to pediatric patients and adults, concentrations in pediatric patients 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.

Patients with Renal Impairment

There is no experience with the use of dexmethylphenidate hydrochloride extended-release capsules in patients with renal impairment. Since renal clearance is not an important route of methylphenidate elimination, renal impairment is expected to have little effect on the pharmacokinetics of dexmethylphenidate hydrochloride extended-release capsules.

Patients with Hepatic Impairment

There is no experience with the use of dexmethylphenidate hydrochloride extended-release capsules in patients with hepatic impairment.

Drug Interaction Studies

Methylphenidate is not metabolized by cytochrome P450 (CYP) isoenzymes to a clinically relevant extent. Inducers or inhibitors of CYPs are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate did not relevantly inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A. Clinically, methylphenidate coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

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 was seen at a daily dose of approximately 60 mg/kg/day. This dose is approximately 2 times the MRHD of 60 mg/day of racemic methylphenidate given to children on a mg/m^2 basis. 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, which is approximately 4 times the MRHD (children) of 60 mg/day of racemic methylphenidate in children on a mg/m^2 basis.

In a 24-week carcinogenicity study with racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female 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, in the *in vitro* mouse lymphoma cell forward mutation assay, or in the *in vivo* mouse bone marrow micronucleus test. In an in vitro assay using cultured Chinese Hamster Ovary cells treated with racemic methylphenidate, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response.

Impairment of Fertility

No human data on the effect of methylphenidate on fertility are available.

Fertility studies have not been conducted with dexmethylphenidate. 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, approximately 10 times the MRHD of 60 mg/day of racemic methylphenidate given to adolescents on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Pediatric Patients

A randomized, double-blind, placebo-controlled, parallel-group study (Study 1) was conducted in 103 pediatric patients (ages 6 to 12, n = 86; ages 13 to 17, n = 17) who met DSM-IV criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive-impulsive subtypes (Study 1).

Patients were randomized to receive either a flexible-dose of dexmethylphenidate hydrochloride extended-release capsules (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 remained on this optimal dose for the last 2 weeks of the study without dose changes or interruption.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for dexmethylphenidate hydrochloride extended-release capsules 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). The CADS-T includes the ADHD Index (12 items) and the DSM-IV total subscale (18 items, total score range: 0 to 54); the latter is divided into inattentive (9 items) and hyperactive-impulsive (9 items) subscales. Teachers assessed behavior observed during the school day by completing the CADS-T weekly. A decrease in the CADS-T DSM-IV total subscale score from baseline indicates improvement.

The CADS-T total scores showed a statistically significant treatment effect in favor of dexmethylphenidate hydrochloride extended-release capsules than placebo (Table 6). There were insufficient adolescents enrolled in this study to assess the efficacy for dexmethylphenidate hydrochloride extended-release capsules in the adolescent population. However, pharmacokinetic considerations and evidence of effectiveness of dexmethylphenidate hydrochloride immediate-release tablets in adolescents support the effectiveness of dexmethylphenidate hydrochloride extended-release capsules in this population.

Table 6: Summary of Efficacy Results from ADHD Study in Pediatric Patients (6 – 17 years) (Study 1)

Study Number	Treatment Group	Primary Efficacy Measure: CADS-T Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	Dexmethylphenidate Hydrochloride Extended-Release Capsules 5-30 mg/day (n = 52)	33.3 (9.18)	16.41 (1.8)	10.64 (5.38, 15.91)
	Placebo (n = 45)	34.9 (10.03)	5.77 (1.93)	--

Abbreviations: ADHD, attention deficit hyperactivity disorder; SD, standard deviation; SE, standard error; LS Mean, least-squares mean; CI, confidence interval, not adjusted for multiple comparisons.

[a]Difference (drug minus placebo) in least-squares mean change from baseline.

In 2 additional cross-over studies (Studies 2 and 3) in pediatric patients ages 6 to 12 years, who received 20 mg dexmethylphenidate hydrochloride extended-release capsules or placebo, dexmethylphenidate hydrochloride extended-release capsules were found to have a statistically significant treatment effect versus placebo on the Swanson, Kotkin, Agler, M-Flynn & Pelham (SKAMP) rating scale total scores at all-time points after dosing in each study (0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours in Study 2 and 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours in the study 3). SKAMP is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. A treatment effect was also observed 0.5 hours after administration of dexmethylphenidate hydrochloride extended-release capsules 20 mg in an additional study of ADHD patients ages 6 to 12 years.

14.2 Adult Patients

A randomized, double-blind, placebo-controlled, parallel-group (Study 4) was conducted in 221 adult patients ages 18 to 60 years who met DSM-IV criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive- impulsive subtypes (Study 4).

Patients were randomized to receive either a fixed dose of dexmethylphenidate hydrochloride extended-release capsules (20, 30, or 40 mg/day) or placebo once daily for 5 weeks. Patients randomized to dexmethylphenidate hydrochloride extended-release capsules 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 capsules 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).

The DSM-IV ADHD-RS is an 18-item questionnaire with a score range of 0 to 54 points that measures the core symptoms of ADHD and includes both hyperactive/impulsive and inattentive subscales.

All 3 dexmethylphenidate hydrochloride extended-release capsules doses (20, 30, and 40 mg/day) showed a statistically significant treatment effect compared to placebo. There was no obvious increase in effectiveness with increasing the dose.

Table 7: Summary of Efficacy Results from ADHD Study in Adults (Study 4)

Study Number	Treatment Group	Primary Efficacy Measure: ADHD-RS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 4	Dexmethylphenidate Hydrochloride Extended-Release Capsules 20 mg/day (n=57)	36.8 (7.2)	13.27 (1.44)	5.71 (1.64, 9.78)
	Dexmethylphenidate Hydrochloride Extended-Release Capsules 30 mg/day (n=54)	36.9 (8.07)	12.86 (1.48)	5.31 (1.18, 9.44)
	Dexmethylphenidate Hydrochloride Extended-Release Capsules 40 mg/day (n=54)	36.9 (8.25)	16.51 (1.48)	8.96 (4.83, 13.08)
	Placebo (n=53)	37.5 (7.82)	7.55 (1.49)	--

Abbreviations: ADHD, attention deficit hyperactivity disorder; SD, standard deviation; SE, standard error; LS Mean, least-squares mean; CI, confidence interval, not adjusted for multiple comparisons.

[a]Difference (drug minus placebo) in least-squares mean change from baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dexmethylphenidate hydrochloride extended-release capsules are available as follows:

- 5 mg Extended-Release Capsules (NDC 57664-621-88) powder blue colored cap and body imprinted with '621' on cap and '5 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 10 mg Extended-Release Capsules (NDC 57664-622-88) yellow colored cap and body imprinted with '622' on cap and '10 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 15 mg Extended-Release Capsules (NDC 57664-623-88) turquoise colored cap and body imprinted with '623' on cap and '15 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 20 mg Extended-Release Capsules (NDC 57664-624-88) white colored cap and body imprinted with '624' on cap and '20 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 25 mg Extended-Release Capsules (NDC 57664-628-88) powder blue colored cap and white colored body imprinted with '628' on cap and '25 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 30 mg Extended-Release Capsules (NDC 57664-625-88) yellow colored cap and white colored body imprinted with '625' on cap and '30 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 35 mg Extended-Release Capsules (NDC 57664-629-88) powder blue colored cap and yellow colored body imprinted with '629' on cap and '35 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.
- 40 mg Extended-Release Capsules (NDC 57664-626-88) turquoise colored cap and white colored body imprinted with '626' on cap and '40 mg' on body in black ink containing white to off-white pellets; supplied in bottles of 100 CRC.

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

Dispense in tight container (USP).

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired dexmethylphenidate hydrochloride extended-release capsules by a medicine take-back program or by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix dexmethylphenidate hydrochloride extended-release capsules with an undesirable, non-toxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard dexmethylphenidate hydrochloride extended-release capsules in the household trash.

17 PATIENT COUNSELING INFORMATION

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

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients that dexmethylphenidate hydrochloride extended-release capsules are a controlled substance, and it can be abused and lead to dependence. Instruct patients that they should not give dexmethylphenidate hydrochloride extended-release capsules to anyone else. Advise patients to store dexmethylphenidate hydrochloride extended-release capsules in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired dexmethylphenidate hydrochloride extended-release capsules by a medicine take-back program if available *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2, 9.3), How Supplied/Storage and Handling (16)]*.

Serious Cardiovascular Risks

Advise patients that there is a potential serious cardiovascular risk, including sudden death, myocardial infarction, stroke, and hypertension with dexmethylphenidate hydrochloride extended-release capsules use. Instruct patients to contact a healthcare provider immediately if they develop symptoms, such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Instruct patients that dexmethylphenidate hydrochloride extended-release capsules can cause elevations of their blood pressure and pulse rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients that dexmethylphenidate hydrochloride extended-release capsules, at recommended doses, can cause psychotic or manic symptoms, even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct them to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

Circulation Problems in Fingers and Toes (Peripheral Vasculopathy, Including Raynaud's Phenomenon)

Instruct patients beginning treatment with dexmethylphenidate hydrochloride extended-release capsules 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 capsules. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients that dexmethylphenidate hydrochloride extended-release capsules may cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to ADHD medications, including dexmethylphenidate hydrochloride extended-release capsules, during pregnancy *[see Use in Specific Populations (8.1)]*.

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