

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
<p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none">CNS stimulants, including dexamethylphenidate 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
<ul style="list-style-type: none">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
<ul style="list-style-type: none">Known hypersensitivity to methylphenidate or other components of dexmethylphenidate hydrochloride extended-release capsules (4).

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: ABUSE AND DEPENDENCE
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Pretreatment Screening
2.2 Treatment of Attention Deficit Hyperactivity Disorder
2.3 Administration Instructions
2.4 Dose Reduction and Discontinuation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Potential for Abuse and Dependence
5.2 Serious Cardiovascular Reactions
5.3 Blood Pressure and Heart Rate Increases
5.4 Psychiatric Adverse Reactions
5.5 Priapism
5.6 Peripheral Vascuopathy, Including Raynaud's Phenomenon
5.7 Long-Term Suppression of Growth
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Clinically Important Drug Interactions with Dexmethylphenidate Hydrochloride Extended-Release Capsules
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

WARNING: ABUSE AND DEPENDENCE
<p>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)].</p>

1 INDICATIONS AND USAGE
Dexmethylphenidate hydrochloride extended-release capsules are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [see <i>Clinical Studies</i> (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 <i>Warnings and Precautions</i> (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 <i>Boxed Warning, Warnings and Precautions</i> (5.1), <i>Drug Abuse and Dependence</i> (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:
<ul style="list-style-type: none">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 – Hard gelatin capsule size “2” light brown cap and white opaque body, imprinted with “M5” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
10 mg extended-release capsules – Hard gelatin capsule size “2” white opaque cap and white opaque body, imprinted with “M10” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
15 mg extended-release capsules – Hard gelatin capsule size “1” yellow opaque cap and white opaque body, imprinted with “M15” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
20 mg extended-release capsules – Hard gelatin capsule size “1” light brown cap and white opaque body, imprinted with “M20” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
25 mg extended-release capsules – Hard gelatin capsule size “0” yellow opaque cap and white opaque body, imprinted with “M25” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
30 mg extended-release capsules – Hard gelatin capsule size “00” white opaque cap and white opaque body, imprinted with “M30” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
35 mg extended-release capsules – Hard gelatin capsule size “00” light yellow opaque cap and light yellow opaque body, imprinted with “M35” on cap and “AC” on body in red ink filled with white to off white spherical pellets.
40 mg extended-release capsules – Hard gelatin capsule size “00” yellow opaque cap and white opaque body, imprinted with “M40” on cap and “AC” on body in black ink filled with white to off white spherical 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 <i>Adverse Reactions</i> (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 <i>Drug Interactions</i> (7.1)].

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.

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.

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.

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.

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15 mg extended-release capsules – Hard gelatin capsule size “1” yellow opaque cap and white opaque body, imprinted with “M15” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
20 mg extended-release capsules – Hard gelatin capsule size “1” light brown cap and white opaque body, imprinted with “M20” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
25 mg extended-release capsules – Hard gelatin capsule size “0” yellow opaque cap and white opaque body, imprinted with “M25” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
30 mg extended-release capsules – Hard gelatin capsule size “00” white opaque cap and white opaque body, imprinted with “M30” on cap and “AC” on body in black ink filled with white to off white spherical pellets.
35 mg extended-release capsules – Hard gelatin capsule size “00” light yellow opaque cap and light yellow opaque body, imprinted with “M35” on cap and “AC” on body in red ink filled with white to off white spherical pellets.
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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)].

5.1 Potential for Abuse and Dependence
CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, other 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 <i>Boxed Warning, Drug Abuse and Dependence</i> (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.

Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4).

5.2 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).
5.3 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).
5.4 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).
5.5 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).
5.6 Peripheral Vascuopathy, Including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vascuopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants (5.6).
5.7 Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients (5.7).

5.2 Lactation
5.3 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).
5.4 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).
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5.6 Peripheral Vascuopathy, Including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vascuopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants (5.6).
5.7 Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients (5.7).

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 Camber Pharmaceuticals, Inc., at 1-866-495-8330, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

14.1 Pediatric Patients

14.2 Adult Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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 Vascuopathy, Including Raynaud's Phenomenon

CNS stimulants, including dexmethylphenidate hydrochloride extended-release capsules, used to treat ADHD are associated with peripheral vascuopathy, 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 vascuopathy, 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 weight 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 Vascuopathy, 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 fixed-dose methylphenidate 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.

System Organ Class	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Placebo
Adverse Reaction	N = 53	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	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Placebo
Adverse Reaction	10 mg/day N = 64	20 mg/day N = 60	30 mg/day N = 58	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	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Placebo
Adverse Reaction	20 mg N = 57	30 mg N = 54	40 mg N = 54	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	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Dexmethylphenidate Hydrochloride Extended-Release Capsules	Placebo
	20 mg (N = 57)	30 mg (N = 54)	40 mg (N = 54)	(N = 53)
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (-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 post approval 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 Ritalin and Dexmethylphenidate Hydrochloride Formulations

The following adverse reactions associated with the use of all Ritalin 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

mg and 40 mg strengths are black iron oxide and potassium hydroxide, 35 mg strength is red iron oxide. Each strength capsule also contains colorant ingredients in the capsule shell as follows:

- 5 mg: FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6 and D&C yellow No. 10
- 10 mg: contains no colorants
- 15 mg: FD&C yellow No. 6 and D&C yellow No. 10
- 20 mg: FD&C red No. 40, FD&C blue No. 1 and D&C yellow No. 10
- 25 mg: FD&C yellow No. 6 and D&C yellow No. 10
- 30 mg: contains no colorants
- 35 mg: iron oxide yellow
- 40 mg: FD&C yellow No. 6 and D&C yellow No. 10

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 does not prolong the QTc interval to any clinically relevant extent.

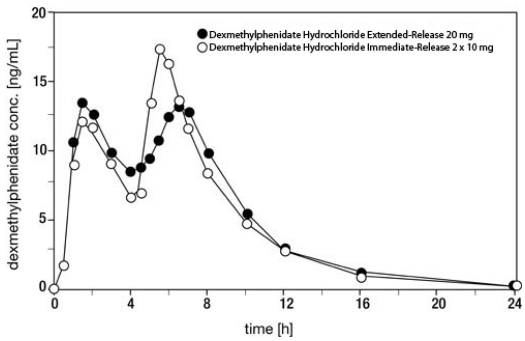
12.3 Pharmacokinetics

Absorption

Dexmethylphenidate hydrochloride extended-release capsules produces 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 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_{min}) is slightly shorter, and time to the second peak (t_{max2}) is slightly longer for dexmethylphenidate hydrochloride extended-release capsules given once daily (about 4.5 to 5.5 hours; range, 4.5 to 7 hours) compared to dexmethylphenidate hydrochloride 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 exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{min}), and fewer peak and trough fluctuations than dexmethylphenidate hydrochloride tablets given in 2 doses 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_{0-24} 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 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) Capsules 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 ± 1.1 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). Methylphenidate 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 *d*-methylphenidate was *d*-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 pediatric 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, 2C9, 2C19, 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/m² 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/m² 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 104 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/m² 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 immediate-release dexmethylphenidate hydrochloride 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* (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. *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* (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.

*Difference (drug minus placebo) in least-squares mean change from baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dexmethylphenidate hydrochloride extended-release capsules are available containing 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg of dexmethylphenidate hydrochloride.

5 mg extended-release capsules are hard gelatin capsule size "2" light brown cap and white opaque body, imprinted with "M5" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-229-01 bottles of 100 capsules

10 mg extended-release capsules are hard gelatin capsule size "2" white opaque cap and white opaque body, imprinted with "M10" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-230-01 bottles of 100 capsules

15 mg extended-release capsules are hard gelatin capsule size "1" yellow opaque cap and white opaque body, imprinted with "M15" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-231-01 bottles of 100 capsules

20 mg extended-release capsules are hard gelatin capsule size "1" light brown cap and white opaque body, imprinted with "M20" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-232-01 bottles of 100 capsules

25 mg extended-release capsules are hard gelatin capsule size "0" yellow opaque cap and white opaque body, imprinted with "M25" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-233-01 bottles of 100 capsules

30 mg extended-release capsules are hard gelatin capsule size "00" white opaque cap and white opaque body, imprinted with "M30" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-234-01 bottles of 100 capsules

35 mg extended-release capsules are hard gelatin capsule size "00" light yellow opaque cap and light yellow opaque body, imprinted with "M35" on cap and "AC" on body in red ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-235-01 bottles of 100 capsules

40 mg extended-release capsules are hard gelatin capsule size "00" yellow opaque cap and white opaque body, imprinted with "M40" on cap and "AC" on body in black ink filled with white to off white spherical pellets. They are available as follows:

NDC 31722-236-01 bottles of 100 capsules

Store at 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense in light 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 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 Warnings, 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)].

Manufactured by:

Ascent Pharmaceuticals, Inc.
Central Islip, NY 11722

Manufactured for:

Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

Rev: 12/21

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JOB SPECIFICATION FORM

Job #:

Customer Name:

Customer Rep:

Date Submitted:

JOB INFO

Job Name:

Type: New Design ()

Reprint ()

File Name:

JOB TYPE: () Insert

() Med Guide

() Patient Guide

Rev:

Proof #:

Grain direction:

Manufacture by:

Manufacture for:

Fold Type:

Flat Size:

Final Folded size:

Finishing For Padding:

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Width: 13.25"
Length: 17.875"
Fold: 1.375" x 1.375"

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 dexamethylphenidate 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).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE AND DEPENDENCE

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

1. Pretreatment Screening
2. Treatment of Attention Deficit Hyperactivity Disorder
3. Administration Instructions
4. Dose Reduction and Discontinuation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vascuopathy, Including Raynaud's Phenomenon
- 5.7 Long-Term Suppression of Growth

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

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 (14.1)*).

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 (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 dose 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 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 pediatric 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 applesauce 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 – Hard gelatin capsule size "2" light brown cap and white opaque body, imprinted with "M5" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 10 mg extended-release capsules – Hard gelatin capsule size "2" white opaque cap and white opaque body, imprinted with "M10" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 15 mg extended-release capsules – Hard gelatin capsule size "1" yellow opaque cap and white opaque body, imprinted with "M15" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 20 mg extended-release capsules – Hard gelatin capsule size "1" light brown cap and white opaque body, imprinted with "M20" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 25 mg extended-release capsules – Hard gelatin capsule size "0" yellow opaque cap and white opaque body, imprinted with "M25" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 30 mg extended-release capsules – Hard gelatin capsule size "00" white opaque cap and white opaque body, imprinted with "M30" on cap and "AC" on body in black ink filled with white to off white spherical pellets.
- 35 mg extended-release capsules – Hard gelatin capsule size "00" light yellow opaque cap and light yellow opaque body, imprinted with "M35" on cap and "AC" on body in red ink filled with white to off white spherical pellets.
- 40 mg extended-release capsules – Hard gelatin capsule size "00" yellow opaque cap and white opaque body, imprinted with "M40" on cap and "AC" on body in black ink filled with white to off white spherical 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.

- 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 Vascuopathy, 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 Camber Pharmaceuticals, Inc., at 1-866-495-8330, 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).
- Halogated 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: 12/21

- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Pediatric Patients
- 14.2 Adult Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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. An 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 Vascuopathy, 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 dexmethylphenidate 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 Vascuopathy, 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

Certain 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 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.

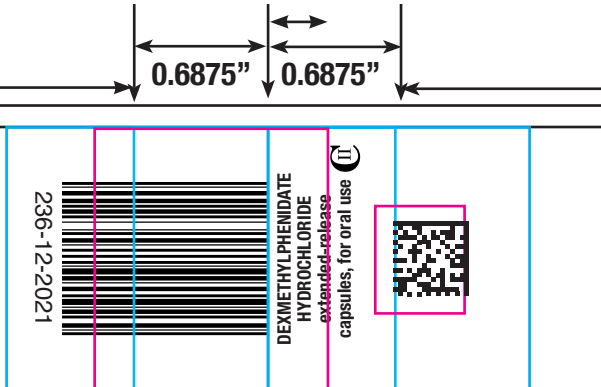


Table 2: Dose-Related Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class	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 Extended-Release Capsules N = 63
Adverse Reaction				
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 Extended-Release Capsules 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 Extended-Release Capsules (N = 53)
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	2.1 ± 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 post approval 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 Ritalin and Dexmethylphenidate Hydrochloride Formulations
The following adverse reactions associated with the use of all Ritalin 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 or to establish a causal relationship to drug exposure.

Infections and Infestations: nasopharyngitis

Blood and the Lymphatic System Disorders: