HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADDERALL XR safely and effectively. See full prescribing information for ADDERALL XR.

ADDERALL XR® (mixed salts of a single-entity amphetamine product) extended-release capsules, for oral use, CII
Initial U.S. Approval: 2001

WARNING: ABUSE, MISUSE, and ADDICTION

See full prescribing information for complete boxed warning.

ADDERALL XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Warnings and Precautions (5.5)	09/2025

----------INDICATIONS AND USAGE----------

ADDERALL XR, a CNS stimulant, is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older. (1)

Limitations of Use

The use of ADDERALL XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage. (5.5, 8.4)

----------DOSAGE AND ADMINISTRATION----------

- Pediatric patients (ages 6 to 17): 10 mg once daily in the morning. Maximum dose for children 6 to 12 years of age is 30 mg once daily. (2.2, 2.3, 2.4)
- Adults: 20 mg once daily in the morning. (2.5)
- Pediatric patients (ages 6 to 17) with severe renal impairment: 5 mg once daily in the morning. Maximum dose for children 6 to 12 years of age with severe renal impairment is 20 mg once daily. (2.6, 8.6)
- Adults with severe renal impairment: 15 mg once daily in the morning. (2.6, 8.6)
- Patients with end stage renal disease (ESRD): Not recommended. (2.6, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity or idiosyncrasy to amphetamine. (4)
- During or within 14 days following the administration of monoamine oxidase inhibitors (MAOI). (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease. (5.2)
- Increased Blood Pressure and Heart Rate: Monitor blood pressure and pulse at appropriate intervals. (5.3)
- Psychiatric Adverse Reactions: Prior to initiating ADDERALL XR, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing ADDERALL XR. (5.4)
- Long-Term Suppression of Growth in Pediatric Patients: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.5)
- Seizures: May lower the convulsive threshold. Discontinue in the presence of seizures. (5.6)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Careful observation for digital changes is necessary during ADDERALL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.7)
- Serotonin Syndrome: Increased risk when coadministered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue ADDERALL XR and initiate supportive treatment. (4, 5.8, 10)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating ADDERALL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.9)

----------ADVERSE REACTIONS----------

- Pediatric patients ages 6 to 12: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. (6.1)
- Pediatric patients ages 13 to 17: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness. (6.1)
- Adults: Most common adverse reactions ≥5% and with a higher incidence than on placebo were dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Alkalinizing agents (GI antacids and urinary): These agents increase blood levels of amphetamine. (2.7, 7.1)
- Acidifying agents (GI and urinary): These agents reduce blood levels of amphetamine. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, and ADDICTION

ADDERALL XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout ADDERALL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

1.1 Attention Deficit Hyperactivity Disorder

ADDERALL XR® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

Limitations of Use

The use of ADDERALL XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.5), Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with ADDERALL XR, assess:

- for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating ADDERALL XR *[see Warnings and Precautions (5.9)]*.

2.2 General Administration Information

Individualize the dosage according to the therapeutic needs and response of the patient. Administer ADDERALL XR at the lowest effective dosage.

Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL, (for example, twice daily), may be switched to ADDERALL XR at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

ADDERALL XR extended-release capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle 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.

ADDERALL XR may be taken orally with or without food.

ADDERALL XR should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

2.3 Recommended Dosage in Pediatric Patients 6 to 12 Years

In pediatric patients 6 to 12 years of age with ADHD and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children 6 to 12 years of age is 30 mg/day; doses greater than 30 mg/day have not been studied in children. ADDERALL XR has not been studied in children under 6 years of age.

2.4 Recommended Dosage in Pediatric Patients 13 to 17 Years

The recommended starting dose for pediatric patients 13 to 17 years of age with ADHD and are either starting treatment for the first time or switching from another medication is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

2.5 Recommended Dosage in Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

2.6 Dosage in Patients with Renal Impairment

In adult patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2), the recommended dose is 15 mg once daily in the morning. In pediatric patients (6 to 17 years of age) with severe renal impairment, the recommended dose is 5 mg once daily. The maximum dose for children 6 to 12 years of age with severe renal impairment is 20 mg once daily. ADDERALL XR is not recommended in patients with end stage renal disease (ESRD) (GFR <15 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.7 Dosage Modification due to Drug Interactions

Agents that alter urinary pH can impact excretion and alter blood levels of amphetamines. Acidifying agents (e.g., ascorbic acid) decrease blood levels; adjust ADDERALL XR dosage based on clinical response *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

ADDERALL XR 5 mg extended-release capsules: Clear/blue (imprinted ADDERALL XR 5 mg)

ADDERALL XR 10 mg extended-release capsules: Blue/blue (imprinted ADDERALL XR 10 mg)

ADDERALL XR 15 mg extended-release capsules: Blue/white (imprinted ADDERALL XR 15 mg)

ADDERALL XR 20 mg extended-release capsules: Orange/orange (imprinted ADDERALL XR 20 mg)

ADDERALL XR 25 mg extended-release capsules: Orange/white (imprinted ADDERALL XR 25 mg)

ADDERALL XR 30 mg extended-release capsules: Natural/orange (imprinted ADDERALL XR 30 mg)

4 CONTRAINDICATIONS

ADDERALL XR administration is contraindicated in patients:

- known to be hypersensitive to amphetamine, or other components of ADDERALL XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products *[see Adverse Reactions (6.2)]*.
- taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Warnings and Precautions (5.8), Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

ADDERALL XR has a high potential for abuse and misuse. The use of ADDERALL XR exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. ADDERALL XR can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2)]*. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store ADDERALL XR in a safe place, preferably locked, and instruct patients to not give ADDERALL XR to anyone else. Throughout ADDERALL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage. Avoid ADDERALL XR use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm).

Monitor all ADDERALL XR-treated patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disease

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating ADDERALL XR treatment, screen patients for risk factors for developing a 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 the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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% of placebo-treated patients. If such symptoms occur, consider discontinuing ADDERALL XR.

5.5 Long-Term Suppression of Growth in Pediatric Patients

ADDERALL XR is not approved for use and is not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in ADDERALL XR-treated pediatric patients treated with CNS stimulants.

In a controlled trial of ADDERALL XR in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and

20 mg ADDERALL XR. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Chronic use of amphetamines can be expected to cause a similar suppression of growth *[see Adverse Reactions (6.1)]*.

Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

5.6 Seizures

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

5.7 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including ADDERALL XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports and at the therapeutic dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during ADDERALL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for ADDERALL XR-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.8 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as MAOIs, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see Drug Interactions (7.1)]*. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism *[see Clinical Pharmacology (12.3)]*. The potential for a pharmacokinetic interaction exists with the coadministration of CYP2D6 inhibitors which may increase the risk with increased exposure to ADDERALL XR. In these situations, consider an alternative nonserotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (7.1)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Concomitant use of ADDERALL XR with MAOI drugs is contraindicated *[see Contraindications (4)]*.

Discontinue treatment with ADDERALL XR and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. Concomitant use of ADDERALL XR with other serotonergic drugs or CYP2D6 inhibitors should be used only if the potential benefit justifies the potential risk. If clinically warranted, consider initiating ADDERALL XR with lower doses, monitoring patients for the emergence of serotonin syndrome during drug initiation or titration, and informing patients of the increased risk for serotonin syndrome.

5.9 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including amphetamine, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating ADDERALL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor ADDERALL XR-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.5)]*
- Seizures *[see Warnings and Precautions (5.6)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.9)]*

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 practice.

The premarketing development program for ADDERALL XR included exposures in a total of 1,315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

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

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse Reactions Leading to Discontinuation of Treatment

In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR-treated patients discontinued due to adverse reactions (including three patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo.

The most frequent adverse reactions leading to discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of children (N=595) were anorexia (loss of appetite) (2.9%),

insomnia (1.5%), weight loss (1.2%), emotional lability (1%), and depression (0.7%). Over half of these patients were exposed to ADDERALL XR for 12 months or more.

In a separate placebo-controlled 4 week study in adolescents with ADHD, five patients (2.1%) discontinued treatment due to adverse events among ADDERALL XR-treated patients (N=233) compared to none who received placebo (N=54). The most frequent adverse event leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of ADDERALL XR-treated patients and at a rate at least twice that of placebo) was insomnia (1.3%, n=3).

In one placebo-controlled 4 week study among adults with ADHD with doses 20 to 60 mg, 23 patients (12.0%) discontinued treatment due to adverse events among ADDERALL XR-treated patients (N=191) compared to one patient (1.6%) who received placebo (N=64). The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of ADDERALL XR-treated patients and at a rate at least twice that of placebo) were insomnia (5.2%, n=10), anxiety (2.1%, n=4), nervousness (1.6%, n=3), dry mouth (1.6%, n=3), anorexia (1.6%, n=3), tachycardia (1.6%, n=3), headache (1.6%, n=3), and asthenia (1.0%, n=2).

Adverse Reactions Occurring in Controlled Trials

Adverse reactions reported in a 3 week clinical trial of children and a 4 week clinical trial in adolescents and adults, respectively, treated with ADDERALL XR or placebo are presented in the tables below.

Table 1: Adverse Reactions Reported by 2% or More of Children (6 to 12 Years Old) Receiving ADDERALL XR with Higher Incidence than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Fever	5%	2%
	Infection	4%	2%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Vomiting	7%	4%
	Nausea	5%	3%
	Dyspepsia	2%	1%
Nervous System	Insomnia	17%	2%
	Emotional Lability	9%	2%
	Nervousness	6%	2%
	Dizziness	2%	0%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2: Adverse Reactions Reported by 5% or More of Adolescents (13 to 17 Years Old) Weighing ≤75 kg/165 lbs Receiving ADDERALL XR with Higher Incidence than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%

Digestive System	Loss of Appetite[b]	36%	2%
Nervous System	Insomnia[b] Nervousness	12% 6%	4% 6%[a]
Metabolic/Nutritional	Weight Loss[b]	9%	0%

Note: The following reactions did not meet the criterion for inclusion in *Table 2* but were reported by 2 to 4% of adolescent patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

* Included doses up to 40 mg.

[a] Appears the same due to rounding.

[b] Dose-related adverse reactions.

Table 3: Adverse Reactions Reported by 5% or More of Adults Receiving ADDERALL XR with Higher Incidence than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR (n=191)	Placebo (n=64)
General	Headache Asthenia	26% 6%	13% 5%
Digestive System	Dry Mouth Loss of Appetite Nausea Diarrhea	35% 33% 8% 6%	5% 3% 3% 0%
Nervous System	Insomnia Agitation Anxiety Dizziness Nervousness	27% 8% 8% 7% 13%	13% 5% 5% 0% 13%[a]
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	10%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following reactions did not meet the criterion for inclusion in *Table 3* but were reported by 2 to 4% of adult patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder (e.g., teeth clenching, tooth infection), emotional lability, libido decreased, somnolence, speech disorder (e.g., stuttering, excessive speech), palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

* Included doses up to 60 mg.

[a] Appears the same due to rounding.

Hypertension

In a controlled 4 week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR-treated patients. Similar results were observed at higher doses *[see Warnings and Precautions (5.2)]*.

In a single-dose pharmacokinetic study in 23 adolescents with ADHD, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender, and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 and 20 mg ADDERALL XR, respectively. Higher single

doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours postdose and, not associated with symptoms.

6.2 Adverse Reactions Associated with the Use of Amphetamine, ADDERALL XR, or Adderall

The following adverse reactions have been identified during postapproval use of amphetamine, ADDERALL XR, or Adderall. 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.

Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Cardiovascular: Palpitations. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, motor and verbal tics, aggression, anger, logorrhea, dermatillomania, paresthesia (including formication), and bruxism.

Endocrine: Impotence, changes in libido, frequent or prolonged erections.

Eye Disorders: Vision blurred, mydriasis.

Gastrointestinal: Unpleasant taste, constipation, intestinal ischemia, and other gastrointestinal disturbances.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Skin: Alopecia.

Vascular Disorders: Raynaud's phenomenon.

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with Amphetamines

Table 4: Drugs Having Clinically Important Interactions with Amphetamines

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
Intervention	Do not administer ADDERALL XR concomitantly or within 14 days after discontinuing MAOI *[see Contraindications (4)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of ADDERALL XR and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during ADDERALL XR initiation or dosage increase. If serotonin syndrome occurs, discontinue ADDERALL XR and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.8)]*.

CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of ADDERALL XR and CYP2D6 inhibitors may increase the exposure of ADDERALL XR compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during ADDERALL XR initiation and after a dosage increase. If serotonin syndrome occurs, discontinue ADDERALL XR and the CYP2D6 inhibitor *[see Warnings and Precautions (5.8), Overdosage (10)]*.
Alkalinizing Agents	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Coadministration of ADDERALL XR and gastrointestinal or urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.
Proton Pump Inhibitors	
Clinical Impact	Time to maximum concentration (T_{max}) of amphetamine is decreased compared to when administered alone.
Intervention	Monitor patients for changes in clinical effect and adjust therapy based on clinical response.

7.2 Drug-Laboratory Test Interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

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 ADDERALL XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/.

Risk Summary

Available data from published epidemiologic studies and postmarketing reports on use of prescription amphetamine in pregnant women have not identified a drug-associated risk of major birth defects and miscarriage *(see Data)*. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers taking amphetamines during pregnancy *(see Clinical Considerations)*.

No apparent effects on morphological development were observed in embryo-fetal development studies, with oral administration of amphetamine to rats and rabbits during organogenesis at doses 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. However, in a pre- and postnatal development study, amphetamine (d- to l- ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *(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

Amphetamines, such as ADDERALL XR, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions, increasing the risk of premature delivery. Infants born to mothers taking amphetamines during pregnancy have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

Animal Data

Amphetamine (d- to l- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD given to adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A study was conducted in which pregnant rats received daily oral doses of amphetamine (d- to l- enantiomer ratio of 3:1) of 2, 6, and 10 mg/kg from gestation Day 6 to lactation Day 20. These doses are approximately 0.8, 2, and 4 times the MRHD of 20 mg/day given to adolescents, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on Day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies from the literature in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d, l-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Based on limited case reports in published literature, amphetamine (d- or d, l-) is present in human milk, at relative infant doses of 2 to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of amphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, advise patients that breastfeeding is not recommended during treatment with ADDERALL XR.

8.4 Pediatric Use

The safety and effectiveness of ADDERALL XR have not been established in pediatric patients less than 6 years of age.

The safety and effectiveness of ADDERALL XR have been established in pediatric patients with ADHD 6 years of age and older.

In studies evaluating extended-release amphetamine products, patients 4 to <6 years of age had higher systemic amphetamine exposures than those observed in older pediatric patients at the same dosage. Pediatric patients 4 to <6 years of age also had a higher incidence of adverse reactions, including weight loss.

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including ADDERALL XR, and pediatric patients aged 6 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5)]*.

Juvenile Animal Toxicity Data

Juvenile rats treated with mixed amphetamine salts early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 6 times the maximum recommended human dose (MRHD) given to children on a mg/m^2 basis. No recovery was seen following a drug-free period. A delay in sexual maturation was observed at a dose approximately 6 times the MRHD given to children on a mg/m^2 basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1) of 2, 6, or 20 mg/kg on Days 7 to 13 of age; from Day 14 to approximately Day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.6, 2, and 6 times the MRHD of 30 mg/day, given to children on a mg/m^2 basis. Postdosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

8.5 Geriatric Use

ADDERALL XR has not been studied in the geriatric population.

8.6 Renal Impairment

Due to reduced clearance of amphetamines in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2), the recommended dose should be reduced. ADDERALL XR is not

recommended in patients with ESRD (GFR <15 mL/min/1.73 m^2) *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

d-Amphetamine is not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ADDERALL XR contains amphetamine, a Schedule II controlled substance.

9.2 Abuse

ADDERALL XR has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. ADDERALL XR can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of amphetamine may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

9.3 Dependence

Physical Dependence

ADDERALL XR may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including ADDERALL XR include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

ADDERALL XR may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.

- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of ADDERALL XR should be considered when treating patients with overdose. D-amphetamine is not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

ADDERALL XR extended-release capsules contain mixed salts of a single-entity amphetamine, a CNS stimulant. ADDERALL XR contains equal amounts (by weight) of four salts: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate and amphetamine (D, L)-aspartate monohydrate. This results in a 3.1:1 mixture of dextro- to levo-amphetamine base equivalent.

The 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg strength extended-release capsules are for oral administration. ADDERALL XR contains two types of drug-containing beads (immediate-release and delayed-release) which prolong the release of amphetamine compared to the Adderall (immediate-release) tablet formulation.

Each capsule contains:

Capsule Strength	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine (D,L)-Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg
d-amphetamine base equivalence	2.4 mg	4.7 mg	7.1 mg	9.5 mg	11.9 mg	14.2 mg
l-amphetamine base equivalence	0.75 mg	1.5 mg	2.3 mg	3.0 mg	3.8 mg	4.5 mg

Inactive Ingredients and Colors

The inactive ingredients in ADDERALL XR extended-release capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

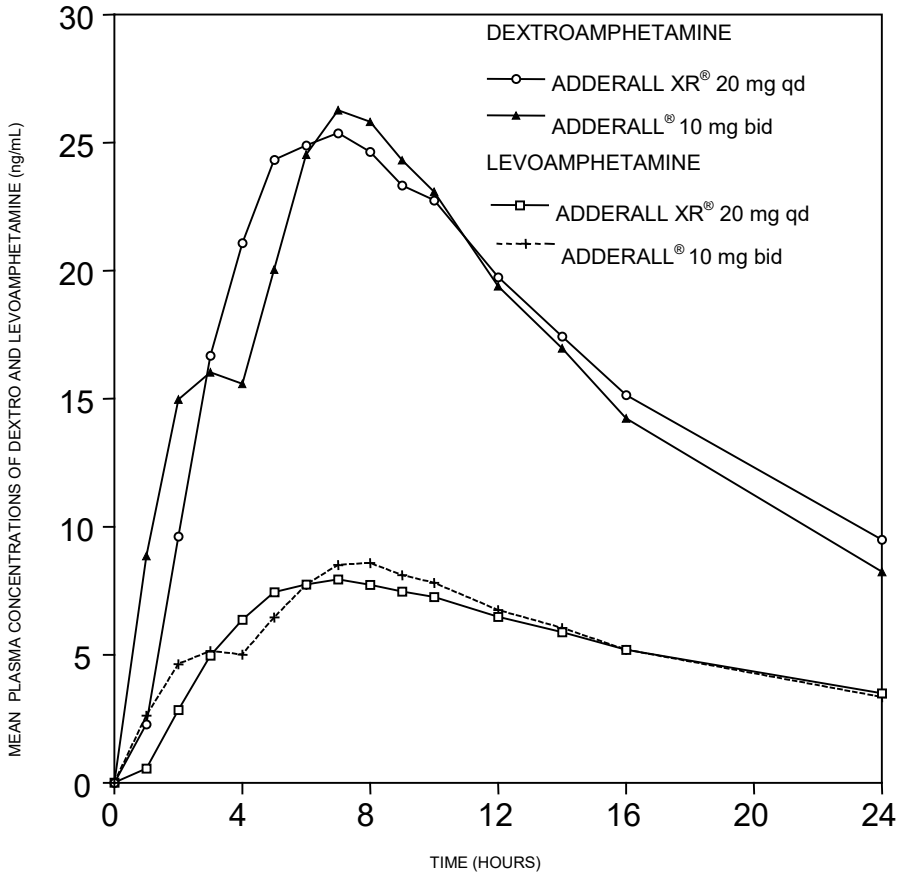
12.3 Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR have been conducted in healthy adult and pediatric (children aged 6 to 12 yrs) subjects, adolescent (13 to 17 yrs), and children with ADHD. Both Adderall (immediate-release) tablets and ADDERALL XR extended-release capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of Adderall (immediate-release),

the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR is about 7 hours, which is about 4 hours longer compared to Adderall (immediate-release). This is consistent with the extended-release nature of the product.

Figure 1: Mean d-amphetamine and l-amphetamine Plasma Concentrations Following Administration of ADDERALL XR 20 mg (8 am) and Adderall (immediate-release) 10 mg Twice Daily (8 am and 12 noon) in the Fed State.



A single dose of ADDERALL XR 20 mg extended-release capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to Adderall (immediate-release) 10 mg twice daily administered 4 hours apart.

The mean elimination half-life for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13 to 17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis, children have a higher clearance than adolescents or adults *(see Special Populations)*.

ADDERALL XR demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents weighing greater than 75 kg/165 lbs, over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.7 hours (from 5.6 hrs at fasted state to 8.3 hrs after a high-fat meal) for l-amphetamine after

administration of ADDERALL XR 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30 to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1 to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased *[see Drug Interactions (7)]*.

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR in children (6 to 12 years) and adolescent (13 to 17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_∞) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_Z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender
Systemic exposure to amphetamine was 20 to 30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race
Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8), and Hispanics (N=10).

Patients with Renal Impairment
The effect of renal impairment on d- and l-amphetamine after administration of ADDERALL XR has not been studied. The impact of renal impairment on the disposition of amphetamine is expected to be similar between oral administration of lisdexamfetamine and ADDERALL XR.

In a pharmacokinetic study of lisdexamfetamine in adult subjects with normal and impaired renal function, mean d-amphetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2). Dialysis did not significantly affect the clearance of d-amphetamine *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No evidence of carcinogenicity was found in studies in which d, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day given to children, on a mg/m^2 basis.

Mutagenesis
Amphetamine, in the enantiomer ratio d- to l- ratio of 3:1, was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility
Amphetamine, in the enantiomer ratio d- to l- ratio of 3:1, did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 8 times the maximum recommended human dose of 20 mg/day given to adolescents, on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d, l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage in rodents. The significance of these findings to humans is unknown.

14 CLINICAL STUDIES

Pediatric Patients
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6 to 12 (N=584) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed-dose treatment groups receiving final doses of 10 mg, 20 mg, or 30 mg of ADDERALL XR or placebo once daily in the morning for three weeks.

Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg, or 30 mg ADDERALL XR demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

A double-blind, randomized, multicenter, parallel-group, placebo-controlled study was conducted in adolescents aged 13 to 17 (N=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤75 kg/165 lbs) were randomized to fixed-dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg ADDERALL XR or placebo once daily in the morning. Patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75 kg/165 lbs who were randomized to fixed-dose treatment groups receiving final doses of 50 mg and 60 mg ADDERALL XR or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV) total score for the primary cohort. The ADHD-RS-IV is an 18- item scale that measures the core symptoms of ADHD. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adult Patients

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed-dose treatment groups receiving final doses of 20 mg, 40 mg, or 60 mg of ADDERALL XR or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD, were observed at endpoint for all ADDERALL XR doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADDERALL XR 5 mg extended-release capsules: Clear/blue (imprinted ADDERALL XR 5 mg), bottles of 100, NDC 54092-381-01

ADDERALL XR 10 mg extended-release capsules: Blue/blue (imprinted ADDERALL XR 10 mg), bottles of 100, NDC 54092-383-01

ADDERALL XR 15 mg extended-release capsules: Blue/white (imprinted ADDERALL XR 15 mg), bottles of 100, NDC 54092-385-01

ADDERALL XR 20 mg extended-release capsules: Orange/orange (imprinted ADDERALL XR 20 mg), bottles of 100, NDC 54092-387-01

ADDERALL XR 25 mg extended-release capsules: Orange/white (imprinted ADDERALL XR 25 mg), bottles of 100, NDC 54092-389-01

ADDERALL XR 30 mg extended-release capsules: Natural/orange (imprinted ADDERALL XR 30 mg), bottles of 100, NDC 54092-391-01

Dispense in a tight, light-resistant container as defined in the USP.

Store at room temperature, 20 to 25ºC (68 to 77ºF). Excursions permitted to 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of ADDERALL XR, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), Overdosage (10)]*. Advise patients to store ADDERALL XR in a safe place, preferably locked, and instruct patients to not give ADDERALL XR to anyone else.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with ADDERALL XR 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)]*.

Increased Blood Pressure and Heart Rate

Advise patients that ADDERALL XR can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Adverse Reactions

Prior to initiating treatment with ADDERALL XR, adequately screen patients with comorbid depressive symptoms to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and/or depression. Additionally, ADDERALL XR therapy at usual doses may cause treatment-emergent psychotic or manic symptoms in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

Instruct patients beginning treatment with ADDERALL XR about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and in 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 ADDERALL XR. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with concomitant use of ADDERALL XR and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid) *[see Contraindications (4), Warnings and Precautions (5.8), Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Concomitant Medications

Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions *[see Drug Interactions (7.1)]*.

Growth
Monitor growth in children during treatment with ADDERALL XR, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5)]*.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome
Advise patients that motor and verbal tics and worsening of Tourette's syndrome may occur during treatment with ADDERALL XR. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.9)]*.

Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADDERALL XR during pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ADDERALL XR. Advise patients of the potential fetal effects from the use of ADDERALL XR during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women not to breastfeed if they are taking ADDERALL XR *[see Use in Specific Populations (8.2)]*.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

For more information call 1-877-825-3327.

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ADL364

MEDICATION GUIDE
ADDERALL XR® (ADD-ur-all X-R)
(mixed salts of a single-entity amphetamine product)
extended-release capsules, CII

What is the most important information I should know about ADDERALL XR?
ADDERALL XR may cause serious side effects, including:
Abuse, misuse, and addiction. ADDERALL XR has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of ADDERALL XR, other amphetamine containing medicines, and methylphenidate containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of ADDERALL XR or when it is used in ways that are not approved, such as snorting or injection.

- Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with ADDERALL XR and will monitor you or your child during treatment.
- ADDERALL XR may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
- Do not give ADDERALL XR to anyone else. See "**What is ADDERALL XR?**" for more information.
- Keep ADDERALL XR in a safe place and properly dispose of any unused medicine. See "**How should I store ADDERALL XR?**" for more information.

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

- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

Your healthcare provider should check you or your child carefully for heart problems before starting treatment with ADDERALL XR. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with ADDERALL XR.

- **Increased blood pressure and heart rate.**

  Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with ADDERALL XR.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior or thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

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

Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with ADDERALL XR, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is ADDERALL XR?
ADDERALL XR is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years of age and older. ADDERALL XR may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
ADDERALL XR is not recommended for use in children under 6 years of age with ADHD.

ADDERALL XR is a federally controlled substance (CII) because it contains amphetamine that can be a target for people who abuse prescription medicines or street drugs. Keep ADDERALL XR in a safe place to protect it from theft. Never give your ADDERALL XR to anyone else because it may cause death or harm them. Selling or giving away ADDERALL XR may harm others and is against the law.

Do not take ADDERALL XR if you or your child:

- are taking or have taken within the past 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid or the intravenous medicine methylene blue.
- are allergic to amphetamine products or any of the ingredients in ADDERALL XR. See the end of this Medication Guide for a complete list of ingredients in ADDERALL XR.

Before taking ADDERALL XR tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide, bipolar illness, or depression
- have kidney problems
- have seizures or have had an abnormal brain wave test (EEG)
- have circulation problems in fingers and toes
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if ADDERALL XR will harm the unborn baby. Tell your healthcare provider if you or your child become pregnant during treatment with ADDERALL XR.
  - There is a pregnancy registry for females who are exposed to ADDERALL XR during pregnancy. The purpose of the registry is to collect information about the health of females exposed to ADDERALL XR and their baby. If you or your child becomes pregnant during treatment with ADDERALL XR, talk to your healthcare provider about registering with the National Pregnancy Registry of Psychostimulants at 1-866-961-2388 or visit online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/.
- are breastfeeding or plan to breastfeed. ADDERALL XR passes into breast milk. You or your child should not breastfeed during treatment with ADDERALL XR. Talk to your healthcare provider about the best way to feed the baby during treatment with ADDERALL XR.

Tell your healthcare provider about all of the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ADDERALL XR and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with ADDERALL XR.

Your healthcare provider will decide if ADDERALL XR can be taken with other medicines.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Know the medicines that you or your child take. Keep a list of your or your child's medicines with you to show your healthcare provider and pharmacist when you or your child get a new medicine.

Do not start any new medicine during treatment with ADDERALL XR without talking to your healthcare provider first.

How should ADDERALL XR be taken?

- Take ADDERALL XR exactly as prescribed by your or your child's healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take ADDERALL XR 1 time each day in the morning when you first wake up.
- ADDERALL XR can be taken with or without food.
- Swallow ADDERALL XR capsules whole. If you or your child cannot swallow the capsule whole, open it and sprinkle the medicine on applesauce.
  - Swallow all of the applesauce and medicine mixture right away.
  - **Do not** chew the applesauce and medicine mixture.
  - **Do not** store the applesauce sprinkled with ADDERALL XR.

If you or your child take too much ADDERALL XR, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of ADDERALL XR?
ADDERALL XR may cause serious side effects, including:

- See **"What is the most important information I should know about ADDERALL XR?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with ADDERALL XR. Your healthcare provider may stop your child's ADDERALL XR treatment if they are not growing or gaining weight as expected.
- **Seizures.** Your healthcare provider may stop treatment with ADDERALL XR if you or your child have a seizure.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon).**
  Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you have or your child have any numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

  Call your healthcare provider right away if you have or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with ADDERALL XR.
- **Serotonin syndrome.** This problem may happen when ADDERALL XR is taken with certain other medicines and may be life-threatening. Stop taking ADDERALL XR and call your healthcare provider or go to the nearest hospital emergency room right away if you or your child develop any of the following signs and symptoms of serotonin syndrome:
  - agitation, hallucinations, coma, or other changes in mental status
  - problems controlling movements or muscle twitching
  - fast heartbeat
  - seizures
  - loss of coordination
  - confusion
  - dizziness
  - change in blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - muscle stiffness or tightness
  - high body temperature (hyperthermia)
- **New or worsening tics or worsening Tourette's Syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with ADDERALL XR.

The most common side effects of ADDERALL XR in children ages 6 to 12 include:

- loss of appetite
- trouble sleeping
- stomach (abdominal) pain
- mood swings
- vomiting
- nervousness
- nausea
- fever

The most common side effects of ADDERALL XR in adolescents ages 13 to 17 include:

- loss of appetite
- trouble sleeping
- stomach (abdominal pain)
- weight loss
- nervousness

The most common side effects of ADDERALL XR in adults include:

- dry mouth
- loss of appetite
- trouble sleeping
- headache
- weight loss
- nausea
- anxiety
- agitation
- dizziness
- fast heartbeat
- diarrhea
- weakness
- urinary tract infections (UTIs)

These are not all the possible side effects of ADDERALL XR.

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 ADDERALL XR?

- Store ADDERALL XR at room temperature between 68 to 77°F (20 to 25°C).
- Protect ADDERALL XR from light.
- Store ADDERALL XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired ADDERALL XR by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix ADDERALL XR 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 ADDERALL XR in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep ADDERALL XR and all medicines out of the reach of children.

General information about the safe and effective use of ADDERALL XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADDERALL XR for a condition for which it was not prescribed. Do not give ADDERALL XR to other people, even if they have the same condition. It may harm them and it is against the law.

You can ask your healthcare provider or pharmacist for information about ADDERALL XR that is written for healthcare professionals.

What are the ingredients in ADDERALL XR?

Active ingredient: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate

Inactive Ingredients: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide

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For more information, you may also contact Takeda Pharmaceuticals (the maker of ADDERALL XR) at 1-877-825-3327 or visit the website at http://www.adderallxr.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. ADL364 Revised: 09/2025