ADDERALL XR® (mixed salts of a single-entity amphetamine product)
dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate capsules, CII

Initial U.S. Approval: 2001

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.

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WARNING: POTENTIAL FOR ABUSE

See full prescribing information for complete boxed warning

• Amphetamines have a high potential for abuse; prolonged administration may lead to dependence. (9)

• Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

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RECENT MAJOR CHANGES

Contraindications (4) 1/2017
Warnings and Precautions (5.6) 1/2017

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INDICATIONS AND USAGE

ADDERALL XR, a CNS stimulant, is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). (1)

• Children (ages 6-12): Efficacy was established in one 3-week outpatient, controlled trial and one analogue classroom, controlled trial in children with ADHD. (14)

• Adolescents (ages 13-17): Efficacy was established in one 4-week controlled trial in adolescents with ADHD. (14)

• Adults: Efficacy was established in one 4-week controlled trial in adults with ADHD. (14)

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DOSE FORM AND STRENGTHS

Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg (3)

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CONTRAINDICATIONS

• Advanced arteriosclerosis (4)

• Symptomatic cardiovascular disease (4)

• Moderate to severe hypertension (4)

• Hyperthyroidism (4)

• Known hypersensitivity or idiosyncrasy to amphetamine (4)

• Glaucoma (4)

• Agitated states (4)

• History of drug abuse (4)

• During or within 14 days following the administration of monoamine oxidase inhibitors (MAOIs) (4, 7.1)

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WARNINGS AND PRECAUTIONS

• Serious Cardiovascular Events: Sudden death has been reported with usual doses of CNS stimulants in children and adolescents with structural cardiac abnormalities, other serious heart problems; sudden death, stroke, and myocardial infarction have been reported in adults taking CNS stimulants at usual doses. Stimulant drugs should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)

• Increase in Blood Pressure: Monitor blood pressure and pulse at appropriate intervals. Use with caution in patients for whom blood pressure increases may be problematic. (5.1)

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ADVERSE REACTIONS

Children (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)

• Adolescents (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)

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DRUG INTERACTIONS

• MAOI antidepressants are contraindicated; MAOIs potentiate the effects of amphetamine. Do not administer ADDERALL XR during or within 14 days after use of MAOI. (4, 7.1).

• Alkalizing agents (GI antacids and urinary): These agents increase blood levels of amphetamine. (7.1)

• Acidifying agents (GI and urinary): These agents reduce blood levels of amphetamine. (7.1)

• Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin, veratrum alkaloids, and ethosuximide: Effects may be reduced by amphetamines. (7.1)

• Tricyclic antidepressants, norepinephrine, and meperidine: Effects may be potentiated by amphetamines. (7.1)

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USE IN SPECIFIC POPULATIONS

• Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus. Based on animal data, may cause fetal harm. (8.1)

• Nursing Mothers: should refrain from breastfeeding. (8.3)

• Pediatric Use: has not been studied in children under 6 years of age. (8.4)

• Geriatric Use: has not been studied in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017
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1 INDICATIONS AND USAGE
1.1 Attention Deficit Hyperactivity Disorder
ADDERALL XR® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

The efficacy of ADDERALL XR in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD [see CLINICAL STUDIES (14)].

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

Special Diagnostic Considerations
Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program
ADDERALL XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician’s assessment of the chronicity and severity of the child’s symptoms.

Long-Term Use
The effectiveness of ADDERALL XR for long-term use, i.e., for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2 DOSAGE AND ADMINISTRATION
2.1 Dosing Considerations for All Patients
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 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 with or without food.

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

Where possible, ADDERALL XR therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

2.2 Children
In children with ADHD who are 6-12 years of age 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 is 30 mg/day; doses greater than 30 mg/day of ADDERALL XR have not been studied in children. ADDERALL XR has not been studied in children under 6 years of age.

2.3 Adolescents
The recommended starting dose for adolescents with ADHD who are 13-17 years of age 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.

2.4 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.

3 DOSAGE FORMS AND STRENGTHS
ADDERALL XR 5 mg capsules: Clear/blue (imprinted ADDERALL XR 5 mg)
ADDERALL XR 10 mg capsules: Orange/orange (imprinted ADDERALL XR 10 mg)
ADDERALL XR 15 mg capsules: Blue/white (imprinted ADDERALL XR 15 mg)
ADDERALL XR 20 mg capsules: Orange/orange (imprinted ADDERALL XR 20 mg)
ADDERALL XR 25 mg capsules: Orange/white (imprinted ADDERALL XR 25 mg)
ADDERALL XR 30 mg capsules: Natural/orange (imprinted ADDERALL XR 30 mg)

4 CONTRAINDICATIONS
ADDERALL XR administration is contraindicated in patients with the following conditions:
• Advanced arteriosclerosis
• Symptomatic cardiovascular disease
• Moderate to severe hypertension
• Hyperthyroidism
• 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)]
• Glaucoma
• Agitated states
• History of drug abuse
• Patients 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) and DRUG INTERACTIONS (7.1)]

5 WARNINGS AND PRECAUTIONS
5.1 Serious Cardiovascular Events
Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems
Children and Adolescents
Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug [see CONTRAINDICATIONS (4)].

Adults
Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs [see CONTRAINDICATIONS (4)].

Hypertension and Other Cardiovascular Conditions
Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia [see CONTRAINDICATIONS (4) and ADVERSE REACTIONS (6)].

Cardiovascular Status in Patients being Treated with Stimulant Medications
Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain,
unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.2 Psychiatric Adverse Events

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

Bipolar Illness
Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms
Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression
Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Long-Term Suppression of Growth

Monitor growth in children during treatment with stimulants. Patients who are not growing or are growing at a slower rate than expected may need to have their treatment interrupted. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In 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.

5.4 Seizures

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

5.5 PerIPHERAL VasculopathY, including RaynauD’s Phenomenon

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, 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.

5.6 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 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 co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to ADDERALL XR. In these situations, consider an alternative non-serotonergic 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.

5.7 Visual Disturbance

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

5.8 Tics

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette’s syndrome. Therefore, clinical evaluation for tics and Tourette’s syndrome in patients and their families should precede use of stimulant medications.

5.9 Prescribing and Dispensing

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. ADDERALL XR should be used with caution in patients who use other sympathomimetic drugs.

6 ADVERSE REACTIONS

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.

6.1 Clinical Studies Experience

The premarketing development program for ADDERALL XR included exposures in a total of 1315 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 3 patients with loss of appetite, one of whom also reported insomnia) compared to 0 in placebo-treated patients.

The most frequent adverse reactions leading to discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of children (N=895) 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 mg 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 asthma (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 (6-12 Years Old) Receiving ADDERALL XR with Higher Incidence Than on Placebo in a 584-Patient Clinical Study

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

Table 2  Adverse Reactions Reported by 5% or More of Adolescents (13-17 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*

*Included doses up to 40 mg
* Appears the same due to rounding
b Dose-related adverse reactions

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.

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*

* Included doses up to 60 mg.
* Appears the same due to rounding

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: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

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

The following adverse reactions have been associated with the use of amphetamine, ADDERALL XR, or ADDERALL:

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, tics, aggression, anger, logorrhea, dermatillomania, paresthesia (including formication), and bruxism.
- Eye Disorders
- Vision blurred, mydriasis.
- Gastrointestinal
- Unpleasant taste, constipation, other gastrointestinal disturbances.
- Allergic
- Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis.
- Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported.
- Endocrine
- Impotence, changes in libido, frequent or prolonged erections.
- Skin
- Alopecia.
- Vascular Disorders
- Raynaud’s phenomenon.
- Musculoskeletal and Connective Tissue Disorders
- Rhabdomyolysis

Hypertension [see WARNINGs AND PRECAUTIONs (5.1)]

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.
7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with Amphetamines

### Table 4: Drugs Having Clinically Important Interactions with Amphetamines

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Class</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td></td>
<td>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.</td>
<td>Do not administer ADDERALL XR concomitantly or within 14 days after discontinuing MAOI (see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.6)).</td>
<td>selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, memantine</td>
</tr>
<tr>
<td>Serotonergic Drugs</td>
<td></td>
<td>The concomitant use of ADDERALL XR and serotonergic drugs increases the risk of serotonin syndrome.</td>
<td>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 (5.6)). and OVERDOSE (10).</td>
<td>selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, trimadlo, tryptophan, buspiro, St. John’s Wort</td>
</tr>
<tr>
<td>CYP2D6 inhibitors</td>
<td></td>
<td>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.</td>
<td>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 CYP2D6 inhibitor (see WARNINGS AND PRECAUTIONS (5.6) and OVERDOSE (10)).</td>
<td>paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir</td>
</tr>
<tr>
<td>Alkalining Agents</td>
<td></td>
<td>Increase blood levels and potentiate the action of amphetamine.</td>
<td>Co-administration of ADDERALL XR and gastrointestinal or urinary alkalining agents should be avoided.</td>
<td>sodium bicarbonate, sodium acetazolamide, some thiazides</td>
</tr>
<tr>
<td>Acidifying Agents</td>
<td></td>
<td>Lower blood levels and efficacy of amphetamines.</td>
<td>Increase dose based on clinical response.</td>
<td>sodium acid phosphate, methenamine salts</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td></td>
<td>May enhance the activity of tricyclic or sympathomimetic agents causing stricking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.</td>
<td>Monitor frequently and adjust or use alternative therapy based on clinical response.</td>
<td>desipramine, protriptyline</td>
</tr>
<tr>
<td>Proton Pump Inhibitors</td>
<td></td>
<td>Time to maximum concentration (TMax) of amphetamine is decreased compared to when administered alone.</td>
<td>Monitor patients for changes in clinical effect and adjust therapy based on clinical response.</td>
<td>omeprazole</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Teratogenic Effects**

Pregnancy Category C.

Amphetamine, in the enantiomer ratio present in ADDERALL XR (d-tol-ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when administered 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) for adolescents of 20 mg/day, on a mg/m² 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 bodyweight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks. 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 in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or f, r), 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.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

8.2 Labor and Delivery

The effects of ADDERALL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

8.4 Pediatric Use

ADDERALL XR is indicated for use in children 6 years of age and older.

The safety and efficacy of ADDERALL XR in children under 6 years of age has not been studied. Long-term effects of amphetamines in children have not been well established. In a juvenile developmental study, rats received daily oral doses of amphetamine (d-tol-ratio of 3:1) from gestation day 6 to postnatal day 20. These doses are approximately 0.8, 2, and 4 times the MRHD for adolescents of 20 mg/day, on a mg/m² 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 bodyweight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks. 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.

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10 OVERDOSE
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggressiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use including ADDERALL XR. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment
Consult a Certified Poison Center for up to date guidance and advice.

The prolonged release of mixed amphetamine salts from ADDERALL XR should be considered when treating patients with overdose.

11 DESCRIPTION
ADDERALL XR is a once daily extended-release, single-entity amphetamine product. ADDERALL XR combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and dl-amphetamine aspartate monohydrate. The ADDERALL XR capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from ADDERALL XR compared to the conventional ADDERALL (immediate-release) tablet formulation.

Each capsule contains: 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
Aspartate Monohydrate 1.25 mg 2.5 mg 3.75 mg 5.0 mg 6.25 mg 7.5 mg
Dextroamphetamine
Sulfate USP 1.25 mg 2.5 mg 3.75 mg 5.0 mg 6.25 mg 7.5 mg
Amphetamine
Sulfate USP 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
Inactive Ingredients and Colors
The inactive ingredients in ADDERALL XR 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 Pharmacokinetics
Pharmacokinetic studies of ADDERALL XR have been conducted in healthy adult and pediatric (children aged 6-12 yrs) subjects, and adolescent (13-17 yrs) and children with ADHD. Both ADDERALL (immediate-release) tablets and ADDERALL XR 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 (Tmax) 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.

A single dose of ADDERALL XR 20 mg 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 13-17 yrs and weighing less than or equal to 75 kg; 10.5 hours in adolescents aged 13-17 yrs and weighing greater than 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 below).

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 increases its oral bioavailability. The absorption of d-amphetamine and l-amphetamine is complete. The time to reach maximum plasma concentration (Tmax) for d-amphetamine and 2.7 hours (from 5.6 hrs at fasted state to 8.3 hrs after a high fat meal) for d-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-hydroxyamphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetaldehyde, 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 exist.

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 predictions 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 30-40% 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 heptatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and its metabolites.

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 (6-12 years) and adolescent (13-17 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 (Cmax) decreased with increases in body weight, while oral volume of distribution (V/F), oral clearance (CL/F), and elimination half-life (t1/2) increased with increases in body weight.

Pediatric Patients
On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life (t1/2) 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 (Cmax 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 20-30% 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 (Cmax 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).

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.
Dispense in a tight, light-resistant container as defined in the USP. Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

17.1 Information on Medication Guide
Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ADDERALL XR and should counsel them in its appropriate use. A patient Medication Guide is available for ADDERALL XR. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Give patients the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

17.2 Controlled Substance Status/Potential for Abuse, Misuse, and Dependence
Advise patients that ADDERALL XR is a federally controlled substance because it can be abused or lead to dependence. Additionally, emphasize that ADDERALL XR should be stored in a safe place to prevent misuse and/or abuse. Evaluate patient history (including family history) of abuse or dependence on alcohol, prescription medicines, or illicit drugs [see DRUG ABUSE AND DEPENDENCE (9)].

17.3 Serious Cardiovascular Risks
Advise patients of serious cardiovascular risk (including sudden death, myocardial infarction, stroke, and hypertension) with ADDERALL XR. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease should stop treatment and undergo prompt evaluation [see WARNINGS AND PRECAUTIONS (5.1)].

17.4 Psychiatric Risks
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 (5.2)].

17.5 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 the 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 or symptoms such as: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red. Instruct patients to report to the emergency room if they experience signs or symptoms of serotonin syndrome.

17.6 Serotonin Syndrome
Caution patients about the risk of serotonin syndrome with concomitant use of SSRI 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 (5.6) and 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.

17.7 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)].

17.8 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 (5.3)].

17.9 Pregnancy
Advise patients to notify their physicians if they become pregnant or intend to become pregnant during treatment [see USE IN SPECIFIC POPULATIONS (8.1)].

17.10 Nursing
Advise patients not to breast feed if they are taking ADDERALL XR [see USE IN SPECIFIC POPULATIONS (8.3)].

17.11 Impairment in Ability to Operate Machinery or Vehicles
ADDERALL XR may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Manufactured for Shire US Inc., 300 Shire Way, Lexington, MA 02421. Made in USA. For more information call 1-800-828-2088

Pharmacist: Medication Guide to be dispensed to patients
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ADDERALL XR® (ADD-ur-all X-R) CII

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

What is the most important information I should know about ADDERALL XR?

1. Heart-related problems:
   - sudden death in patients who have heart problems or heart defects
   - stroke and heart attack in adults
   - increased blood pressure and heart rate
Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor should check you or your child carefully for heart problems before starting ADDERALL XR.

2. Mental (Psychiatric) problems:
   - new or worse behavior and thought problems
   - new or worse bipolar illness
   - new or worse aggressive behavior or hostility
   - new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms
Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

3. Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud’s phenomenon]:
   - Fingers or toes may feel numb, cool, painful
   - Fingers or toes may change from pale, to blue, to red
Tell your doctor if you have or your child has numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

What Is ADDERALL XR?
ADDERALL XR is a once daily central nervous system stimulant prescription medicine. It is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). ADDERALL XR may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

ADDERALL XR has not been studied in children less than 6 years old.
ADDERALL XR may not be right for you or your child. Before starting ADDERALL XR tell you or your child’s doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette’s syndrome
- liver or kidney problems
- thyroid problems
- seizures or have had an abnormal brain wave test (EEG)
- circulation problems in fingers and toes

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

Can ADDERALL XR be taken with other medicines?
Tell your doctor about all of the medicines that you or your child takes including prescription and non-prescription 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 adjusted while taking ADDERALL XR.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- anti-psychotic medicines
- lithium
- narcotic pain medicines
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- stomach acid medicines
- cold or allergy medicines that contain decongestants

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

ADDERALL XR should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

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

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

Who should not take ADDERALL XR?

ADDERALL XR should not be taken if you or your child:

- have heart disease or hardening of the arteries
- have moderate to severe high blood pressure
- have hyperthyroidism
- have an eye problem called glaucoma
- are very anxious, tense, or agitated
- have a history of drug abuse
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- is sensitive to, allergic to, or had a reaction to other stimulant medicines

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- lithium
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- seizure medicines
- blood thinner medicines
- blood pressure medicines
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Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.
Do not start any new medicine while taking ADDERALL XR without talking to your doctor first.

How should ADDERALL XR be taken?

- **Take ADDERALL XR exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Take ADDERALL XR once a day in the morning when you first wake up. ADDERALL XR is an extended release capsule. It releases medicine into your body throughout the day.
- Swallow ADDERALL XR capsules whole with water or other liquids. If you or your child cannot swallow the capsule, open it and sprinkle the medicine over a spoonful of applesauce. Swallow all of the applesauce and medicine mixture without chewing immediately. Follow with a drink of water or other liquid. Never chew or crush the capsule or the medicine inside the capsule.
- ADDERALL XR can be taken with or without food.
- From time to time, your doctor may stop ADDERALL XR treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking ADDERALL XR. Children should have their height and weight checked often while taking ADDERALL XR. ADDERALL XR treatment may be stopped if a problem is found during these check-ups.
- If you or your child takes too much ADDERALL XR or overdoses, call your doctor or poison control center right away, or get emergency treatment.

What are possible side effects of ADDERALL XR?

See “What is the most important information I should know about ADDERALL XR?” for information on reported heart and mental problems.

**Other serious side effects include:**
- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

**Common side effects include:**
- headache
- stomach ache
- trouble sleeping
- weight loss
- dry mouth
- decreased appetite
- nervousness
- mood swings
- dizziness
- fast heart beat

ADDERALL XR may affect you or your child’s ability to drive or do other dangerous activities.

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

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

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 in a safe place at room temperature, 59 to 86°F (15 to 30°C).
- Keep ADDERALL XR and all medicines out of the reach of children.