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: 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.

Dosage and Administration (2.5) 7/2018

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)

DOSEAGE AND ADMINISTRATION

• Pediatric patients (ages 6-12): 10 mg once daily in the morning. Maximum dose for children 6-12 years of age is 30 mg once daily. (2.1, 2.2, 2.3)
• Adults: 20 mg once daily in the morning. (2.4)
• Pediatric patients (ages 6-17) with severe renal impairment: 5 mg once daily in the morning. Maximum dose for children 6-12 years of age with severe renal impairment is 20 mg once daily. (2.5, 8.6)
• Adults with severe renal impairment: 15 mg once daily in the morning. (2.5, 8.6)
• Patients with ESRD: not recommended. (2.5, 8.6)

DOSEAGE FORM AND STRENGTHS

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

CONTRAINDICATIONS

• Advanced arteriosclerosis (4)
• Symptomatic cardiovascular disease (4)
• Moderate to severe hypertension (4)
• Hyperthyroidism (4)
• Known hypersensitivity or idiosyncrasy to amphetamine (4)
• Glaucouma (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)

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 or 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)
• Psychiatric Adverse Events: Stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. Monitor for aggressive behavior. (5.2)
• Long-term Suppression of Growth: Monitor height and weight at appropriate intervals. (5.3)
• Seizures: May lower the convulsive threshold. Discontinue in the presence of seizures. (5.4)
• Peripheral Vasculopathy, including Raynaud's phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital is necessary during treatment with ADHD stimulants. (5.5)
• Serotonin Syndrome: Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRs, triptans), but also during overdosage situations. If it occurs, discontinue ADDERALL XR and initiate supportive treatment (4, 5.6, 10).
• Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.7)
• Tics: May exacerbate tics. Evaluate for tics and Tourette’s syndrome prior to stimulant administration. (5.8)

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)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

• MAOIs 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)

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: 7/2018
FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL FOR ABUSE

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Pay particular attention to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly [see DRUG ABUSE AND DEPENDENCE (9)].

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

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; blurtting 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 6 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 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 sprinkle 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 insomnia.

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 6-12 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.

2.3 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 20 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.

2.5 Dosage in Patients with Renal Impairment

In adult patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73m²), 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/1.73m²] [see USE IN SPECIFIC POPULATIONS (8.6), CLINICAL PHARMACOLOGY (12.3)].

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/blue (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 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 (5.6) 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)].

5.4 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.

5.5 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., rheumatologic referral) may be appropriate for certain patients.

5.6 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are combined in 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 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 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 MAOIs 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 premarking 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 and one double-blind, 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 anemia) compared to 2.7% (7/258) receiving placebo. The most frequent adverse reactions leading to discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of children (N=956) 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 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 (6-12 Years Old) Receiving ADDERALL XR with Higher Incidence Than 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>Accidential 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*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>ADDERALL XR (n=233)</th>
<th>Placebo (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Abdominal Pain (stomachache)</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Digestive System</td>
<td>Loss of Appetite b</td>
<td>36%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Insomnia b</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Nervousness b</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Metabolic/Nutritional</td>
<td>Weight Loss</td>
<td>9%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Includes doses up to 40 mg

### 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*

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

*Includes doses up to 60 mg.

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, dysmennorhea, and impotence.

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.

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 mg 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 post dose and not associated with symptoms.

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

- Cardiac: 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.
Table 4: Drugs Having Clinically Important Interactions with Amphetamines

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine Oxidase Inhibitors</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 MAO [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.6)].</td>
<td>selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue</td>
</tr>
<tr>
<td>Serotonergic Drugs</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)].</td>
<td>selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John’s Wort</td>
</tr>
<tr>
<td>CYP2D6 Inhibitors</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 and after a dosage increase. If serotonin syndrome occurs, discontinue ADDERALL XR and the CYP2D6 inhibitor [see WARNINGS AND PRECAUTIONS (5.6) and OVERDOSAGE (10)].</td>
<td>paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir</td>
</tr>
<tr>
<td>Alkalizing Agents</td>
<td>Increase blood levels and potentiate the action of amphetamine.</td>
<td>Co-administration of ADDERALL XR and gastrointestinal or urinary alkalizing agents should be avoided.</td>
<td>Gastrointestinal alkalizing agents (e.g., sodium bicarbonate). Urinary alkalizing agents (e.g. acetazolamide, some thiazides).</td>
</tr>
<tr>
<td>Acidifying Agents</td>
<td>Lower blood levels and efficacy of amphetamines.</td>
<td>Increase dose based on clinical response.</td>
<td>Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid). Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methamphetamine salts).</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>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.</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>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- to l- ratio of approximately 3:1), had no apparent effects on embryofetal morphological development or survival when orally 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/kg/day, on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following maternal administration of d-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD for adolescents on a mg/m² 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, the same as in ADDERALL XR) 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 for adolescents of 20 mg/kg/day, on a mg/m² basis. All doses caused hypertactivity 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 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.

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 prematurity 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 have 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- to l- enantiomer ratio of 3:1, the same as in ADDERALL XR) of 2, 6, and 20 mg/kg on days 7-13 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 maximum recommended human dose for children of 30 mg/day, on a mg/m² basis. Post dosing 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 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 mL/min/1.73 m²), the recommended dose should be reduced. ADDERALL XR is not recommended in patients with ESRD (GFR < 15 mL/min/1.73 m²) [see DOSAGE and ADMINISTRATION (2.5), CLINICAL PHARMACOLOGY (12.3)]. d-Amphetamine is not dialyzable.
9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
ADDERALL XR is a Schedule II controlled substance.

9.2 Abuse and Dependence
Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have continued chronic amphetamine use despite inadequately supervised withdrawal attempts.

Amphetamines have a high potential for abuse and dependence. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

10 OVERDOSE
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, 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 and tachycardia. Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment
Consult with a Certified Poison Control 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.

d-Amphetamine is not dialyzable.

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 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:

<table>
<thead>
<tr>
<th>Capsule Strength</th>
<th>Dextroamphetamine</th>
<th>Amphetamine (D,L)-Saccharate</th>
<th>Amphetamine (D,L)-Aspartate Monohydrate</th>
<th>Dextroamphetamine Sulfate</th>
<th>Amphetamine Sulfate</th>
<th>Total amphetamine base equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>1.25 mg</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>3.1 mg</td>
</tr>
<tr>
<td>10 mg</td>
<td>2.5 mg</td>
<td>5.0 mg</td>
<td>5.0 mg</td>
<td>5.0 mg</td>
<td>5.0 mg</td>
<td>6.3 mg</td>
</tr>
<tr>
<td>15 mg</td>
<td>3.75 mg</td>
<td>7.5 mg</td>
<td>7.5 mg</td>
<td>7.5 mg</td>
<td>7.5 mg</td>
<td>9.4 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>5.0 mg</td>
<td>10.0 mg</td>
<td>10.0 mg</td>
<td>10.0 mg</td>
<td>10.0 mg</td>
<td>12.5 mg</td>
</tr>
<tr>
<td>25 mg</td>
<td>6.25 mg</td>
<td>12.5 mg</td>
<td>12.5 mg</td>
<td>12.5 mg</td>
<td>12.5 mg</td>
<td>15.6 mg</td>
</tr>
<tr>
<td>30 mg</td>
<td>7.5 mg</td>
<td>15.0 mg</td>
<td>15.0 mg</td>
<td>15.0 mg</td>
<td>15.0 mg</td>
<td>18.8 mg</td>
</tr>
</tbody>
</table>

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

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. ADDERALL XR (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.
Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR in children (6-12 years) and adolescents (13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent elimination rate constant 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/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 (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.

**Race**

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=53), 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 <30mL/min/1.73m²). Dialysis did not significantly affect the clearance of d-amphetamine. [See USE IN SPECIFIC POPULATIONS (8.6)].

**NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No evidence of carcinogenicity was found in studies in which d-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 for children of 30 mg/day, on a mg/m² body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL XR (d- to l- ratio of approximately 3:1), was not clastogenic in the mouse bone marrow micronucleus test in vivo. When tested in the Ehrlich ascites carcinoma 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.

Amphetamine, in the enantiomer ratio present in ADDERALL XR (d- to l- ratio of approximately 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 for adolescents of 20 mg/day, on a mg/m² body surface area 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 6-12 (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, 20, 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 treated with 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, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 (N=327) who met DSM-IV criteria for ADHD. The primary cohort of patients (n=287, weighing >75kg/165lbs) was 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. The secondary cohort consisted of 40 subjects weighing 75kg/165lbs 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 four weeks. Significant improvements, measured with 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 no 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, 40, 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 no adequate evidence that doses greater than 20 mg/day conferred additional benefit.

**15 HOW SUPPLIED/STORAGE AND HANDLING**

ADDERALL XR 5 mg extended release capsules: Clean/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 °C to 25 °C (68 °F to 77 °F). Excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]

**17 PATIENT COUNSELING INFORMATION**

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

**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.

**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)].

**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 chest pain or syncope, or other symptoms suggestive of cardiac disease during treatment should undergo a prompt cardiac evaluation [see WARNINGS AND PRECAUTIONS (5.1)].

**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)]. 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 (5.5)].

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 (5.6) 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.

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 (5.3)].

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)].

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

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.

For more information call 1-800-828-2088
Pharmacist: Medication Guide to be dispensed to patients
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ADDERALL® is a registered trademark of Shire LLC, under license to Duramed Pharmaceuticals, Inc.
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Rev. 7/2018  S43235
What is the most important information I should know about ADDERALL XR?

ADDERALL XR is a stimulant medicine. The following have been reported with use of stimulant medicines.

1. Heart-related problems:
   - sudden death in patients who have heart problems or heart defects
   - stroke and heart attack in adults
   - increased blood pressure and heart rate

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

Your doctor should check you or your child carefully for heart problems before starting ADDERALL XR.

Your doctor should check you or your child's blood pressure and heart rate regularly during treatment with ADDERALL XR.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking ADDERALL XR.

2. Mental (Psychiatric) problems:

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

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

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

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking ADDERALL XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

3. Circulation problems in fingers and toes (Peripheral vasculopathy, including Raynaud's phenomenon):
   - Fingers or toes may feel numb, cool, painful
   - 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.

Call your doctor right away if you have or your child has any unexplained wounds appearing on fingers or toes while taking ADDERALL XR.

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.
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.

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 extended release 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 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
- fast heart beat
- decreased appetite
- nervousness
- mood swings
- dizziness

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