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) dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate capsules, 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.

-----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)

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

- Pediatric patients (ages 6-17): 10 mg once daily in the morning. The maximum dose for children 6-12 is 30 mg once daily. (2.1, 2.2, 2.3)
- Adults: 20 mg once daily in the morning. (2.4)

-----DOSAGE FORM AND STRENGTHS-----

- 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 the sympathomimetic amines (4)
- Glaucoma (4)
- Agitated states (4)
- History of drug abuse (4)
- During or within 14 days following the administration of monoamine oxidase inhibitors (MAOI) (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)
- Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.5)
- Tics: May exacerbate tics. Evaluate for tics and Tourette's syndrome prior to stimulant administration. (5.6)

-----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-----

- 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).
- Alkalinizing 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. (7.2)
- Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin, veratrum alkaloids, and ethosuximide: Effects may be reduced by amphetamines. (7.3)
- Tricyclic antidepressants, norepinephrine, and meperidine: Effects may be potentiated by amphetamines. (7.4)

-----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: 02/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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; blurting 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 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 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: Blue/blue (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
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines (e.g., anaphylaxis, angioedema, serious skin rashes) *[see ADVERSE REACTIONS (6.2)]*
- Glaucoma
- Agitated states
- History of drug abuse
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result) *[see 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)]*.

Assessing 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 gaining weight as 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 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 Visual Disturbance

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

5.6 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.

5.7 Prescribing and Dispensing

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. 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 Trial 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 2.7% (7/259) receiving placebo.

The most frequent adverse reactions leading to discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of children (N=595) were anorexia (loss of appetite) (2.9%), insomnia (1.5%), weight loss (1.2%), emotional lability (1%), and depression (0.7%). Over half of these patients were exposed to ADDERALL XR for 12 months or more.

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

In one placebo-controlled 4-week study among adults with ADHD with doses 20 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 on Placebo in a 584-Patient Clinical Study

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

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*

Body System	Preferred Term	ADDERALL XR (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite[b]	36%	2%
Nervous System	Insomnia[b]	12%	4%
	Nervousness	6%	6%[a]
Metabolic/Nutritional	Weight Loss[b]	9%	0%

*Included doses up to 40 mg

[a] 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*

Body System	Preferred Term	ADDERALL XR (n=191)	Placebo (n=64)
General	Headache	26%	13%
	Asthenia	6%	5%
Digestive System	Dry Mouth	35%	5%
	Loss of Appetite	33%	3%
	Nausea	8%	3%
	Diarrhea	6%	0%
Nervous System	Insomnia	27%	13%
	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

*Included 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, dysmenorrhea, 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

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.

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.

Skin

Alopecia.

7 DRUG INTERACTIONS

7.1 Agents that Increase Blood Levels of Amphetamines

MAO Inhibitors

MAOI antidepressants slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. Do not administer ADDERALL XR during or within 14 days following the administration of monoamine oxidase inhibitors *[see CONTRAINDICATIONS (4)]*

Alkalinizing Agents

Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) increase absorption of amphetamines. Co-administration of ADDERALL XR and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

7.2 Agents that Lower Blood Levels of Amphetamines

Acidifying Agents

Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid) lower absorption of amphetamines. Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

7.3 Agents Whose Effects May be Reduced by Amphetamines

Adrenergic Blockers

Amphetamines may reduce the cardiovascular effects of adrenergic blockers.

Antihistamines

Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives

Amphetamines may antagonize the hypotensive effects of antihypertensives.

Veratrum alkaloids

Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Phenobarbital

Amphetamines may delay intestinal absorption of phenobarbital.

Phenytoin

Amphetamines may delay intestinal absorption of phenytoin.

Ethosuximide

Amphetamines may delay intestinal absorption of ethosuximide.

7.4 Agents Whose Effects May be Potentiated by Amphetamines

Antidepressants, Tricyclic

Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

Meperidine

Amphetamines potentiate the analgesic effect of meperidine.

Norepinephrine

Amphetamines may enhance the adrenergic effect of norepinephrine.

7.5 Agents that May Reduce the Effects of Amphetamines

Chlorpromazine

Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines.

Haloperidol

Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium Carbonate

The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

7.6 Agents that May Potentiate the Effects of Amphetamines

Norepinephrine

Norepinephrine may enhance the adrenergic effect of amphetamine.

Propoxyphene Overdosage

In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

7.7 Proton Pump Inhibitors (PPI)

PPIs act on proton pumps by blocking acid production, thereby reducing gastric acidity. When ADDERALL XR (20 mg single-dose) was administered concomitantly with the proton pump inhibitor, omeprazole (40 mg once daily for 14 days), the median Tmax of *d*-amphetamine was decreased by 1.25 hours (from 4 to 2.75 hours), and the median Tmax of *l*-amphetamine was decreased by 2.5 hours (from 5.5 to 3 hours), compared to ADDERALL XR administered alone. The AUC and C_{max} of each moiety were unaffected. Therefore, co-administration of ADDERALL XR and proton pump inhibitors should be monitored for changes in clinical effect.

7.8 Drug-Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C.

Amphetamine, in the enantiomer ratio present in ADDERALL XR (d- to l- ratio of 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/day, on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD for adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A study was conducted in which pregnant rats received daily oral doses of amphetamine (d- to l- enantiomer ratio of 3:1, 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/day, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup 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 d, l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

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 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, or 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/m^2 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 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

8.5 Geriatric Use

ADDERALL XR has not been studied in the geriatric population.

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 increased the dosage to levels many times higher than recommended. 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 OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms
Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. 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 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.

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 d,l-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. 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.

12.3 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 (T_{max}) for ADDERALL XR is about 7 hours, which is about 4 hours longer compared to ADDERALL (immediate-release). This is consistent with the extended-release nature of the product.

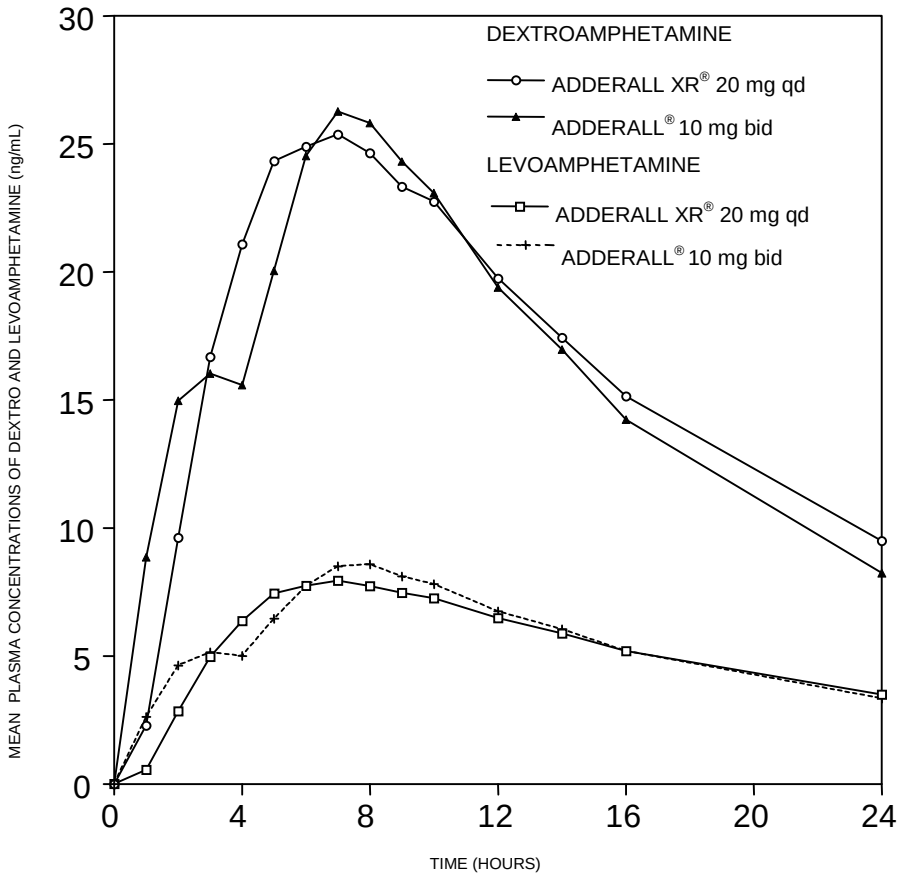

Figure 1 Mean d-amphetamine and l-amphetamine Plasma Concentrations Following Administration of ADDERALL XR 20 mg (8 am) and ADDERALL (immediate-release) 10 mg Twice Daily (8 am and 12 noon) in the Fed State.

A single dose of ADDERALL XR 20 mg 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 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis, children have a higher clearance than adolescents or adults (see Special Populations 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 prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l-amphetamine after

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

Metabolism and Excretion

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

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

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

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR in children (6-12 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 (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_Z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

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

Gender

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

Race

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

A double-blind, randomized, 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. Patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >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 4 weeks. The primary efficacy variable was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV) total score for the primary cohort. The ADHD-RS-IV is an 18-item scale that measures the core symptoms of ADHD. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adult Patients

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed-dose treatment groups receiving final doses of 20, 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 not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

ADDERALL XR 30 mg 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 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

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 during treatment should undergo a prompt cardiac 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 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)]*.

17.6 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)]*.

17.7 Nursing

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

17.8 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., Wayne, PA 19087. Made in USA.

For more information call 1-800-828-2088

Pharmacist: Medication Guide to be dispensed to patients

ADDERALL XR® is registered in the US Patent and Trademark Office

ADDERALL® is a registered trademark of Shire LLC, under license to Duramed Pharmaceuticals, Inc.

Rev. **02/2012**