

PRODUCT MONOGRAPH



mixed salts amphetamine extended-release Capsules

5mg, 10mg, 15mg, 20mg, 25mg, 30mg Capsules

Central Nervous System Stimulant

for Attention Deficit Hyperactivity Disorder

Shire Canada Inc.
Saint- Laurent, Quebec
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CNS Stimulant

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ACTION AND CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (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.

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR (mixed salts amphetamine extended-release capsules) have been conducted in healthy adult and pediatric (aged 6-12 years) subjects, and adolescent (aged 13-17 years) and pediatric patients with ADHD. ADDERALL XR capsules contain dextroamphetamine (*d*-amphetamine) and levoamphetamine (*l*-amphetamine) salts in the ratio of 3:1.

ADDERALL XR demonstrates linear pharmacokinetics over the dose range of 20 to 60mg in adults and adolescents aged 13 to 17 years weighing greater than 75kg/165lbs, over the dose range of 10 to 40mg in adolescents weighing less than or equal to 75kg/165lbs and 5 to 30mg in children aged 6 to 12 years. There was no unexpected accumulation at steady state.

Comparison of the pharmacokinetics of *d*- and *l*-amphetamine after oral administration of ADDERALL XR in pediatric (aged 6-12 years) and adolescent (aged 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.

Pharmacokinetic Results in Healthy Adult and Pediatric Subjects

Following oral administration of a single dose of ADDERALL XR in healthy adult subjects, peak plasma concentrations (C_{max}) of 28.1ng/mL and 8.7ng/mL occurred in about 7 hours for *d*-amphetamine and 8 hours for *l*-amphetamine, respectively. The AUC_{0-inf} for *d*-amphetamine and *l*-amphetamine were 567ng•hr/mL and 203ng•hr/mL, respectively.

The mean elimination half-life is 1 hour shorter for *d*-amphetamine and 2 hours shorter for *l*-amphetamine in children aged 6 to 12 years compared to that in adults ($t_{1/2}$ is 10 hours for *d*-amphetamine and 13 hours for *l*-amphetamine in adults, and 9 hours and 11 hours, respectively, for children). 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.

Pharmacokinetic Results in Children and Adolescents with ADHD

In a 20 mg single dose study in 51 children (aged 6-12 years) with ADHD, the mean T_{max} for *d*-amphetamine was 6.8 hours and the mean C_{max} was 48.8ng/mL. The corresponding mean T_{max} and C_{max} values for *l*-amphetamine were 6.9 hours and 14.8ng/mL, respectively. The mean elimination half-life for *d*-amphetamine and *l*-amphetamine was 9.5 and 10.9 hours, respectively. Following dosing of children with ADHD to steady state with ADDERALL XR 10, 20 and 30mg, the mean *d*-amphetamine C_{max} (ng/mL) in plasma for ADDERALL XR was 28.8 (10mg), 54.6 (20mg) and 89.0 (30mg). For *l*-amphetamine, the mean C_{max} values for the three ADDERALL XR doses were 8.8, 17.2 and 28.1ng/mL, respectively.

In adolescents aged 13-17 years and weighing less than or equal to 75kg/165lbs, the mean elimination half-life for *d*-amphetamine is 11 hours, and 13-14 hours for *l*-amphetamine.

Metabolism

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.

Excretion

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 PRECAUTIONS – Drug Interactions).

Food Effect Study in Healthy Adult Subjects

A single-dose study compared the relative bioavailability of *d*-amphetamine and *l*-amphetamine following administration of a single 30mg dose of ADDERALL XR fasted, fed (high-fat meal) and sprinkled on food (otherwise fasted) in 21 healthy adult subjects. Food does not affect the extent of absorption of ADDERALL XR capsules, but prolongs T_{max} by 2.5 hours (from 5.2 hours at fasted state to 7.7 hours after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted states.

Clinical Trials

Children

A double-blind, randomized, placebo-controlled, parallel-group study of 584 children aged 6 to 12 years who met DSM-IV criteria for ADHD (either combined type or hyperactive-impulsive type) was conducted in a naturalistic setting. Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30mg/day of ADDERALL XR or placebo. ADDERALL XR or placebo was taken once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher and parent 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 titration dose of 10mg/day. Patients who received ADDERALL XR showed behavioral improvements within the first week of treatment ($p < 0.001$) and in both morning ($p < 0.001$) and afternoon ($p < 0.001$) compared to patients on placebo.

A double-blind, randomized, placebo- and active-controlled crossover study of 51 children aged 6 to 12 years with ADHD was conducted in a classroom laboratory setting. In comparison to placebo, ADDERALL XR 10, 20, and 30mg/day showed rapid improvement and continued significant efficacy ($p < 0.05$) up to 12 hours post-dose for all cognitive and behavioral measures.

In these two clinical trials conducted in different settings, ADDERALL XR taken once in the morning demonstrated efficacy in the treatment of ADHD (either combined type or hyperactive-impulsive type) for at least 12 hours.

Adolescents

A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 years ($n=327$) who met DSM-IV® criteria for ADHD. The primary cohort of patients ($n=287$, weighing $\leq 75\text{kg}/165\text{lbs}$) was randomized to fixed dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10mg, 20mg, 30mg, and 40mg ADDERALL XR or placebo once daily in the morning; patients randomized to doses greater than 10mg were titrated to their final doses by 10mg each week. The secondary cohort consisted of 40 subjects weighing $>75\text{kg}/165\text{lbs}$ who were randomized to fixed dose treatment groups receiving final doses of 50mg

and 60mg ADDERALL XR or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the ADHD-RS-IV total scores for the primary cohort. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR 10mg, 20mg, 30mg, and 40mg) compared with the placebo group. ADDERALL XR at doses of 10-40mg is effective in the treatment of ADHD in adolescents weighing $\leq 75\text{kg}/165\text{lbs}$. There was not adequate evidence that doses greater than 20mg/day conferred additional benefit.

Adults

A double-blind, randomized, placebo-controlled, parallel-group study of 255 adults who met DSM-IV criteria for ADHD was conducted. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40 or 60mg/day of ADDERALL XR or placebo. ADDERALL XR or placebo was taken once daily in the morning for four weeks. Significant improvements in patient symptoms of inattention and impulsivity/hyperactivity, based upon the 18-item total ADHD symptom score, were observed at endpoint for all ADDERALL XR doses compared to patients who received placebo for all four weeks ($p < 0.001$). There was not adequate evidence that doses greater than 20mg/day conferred additional benefit.

A long-term, open-label extension of the above-mentioned clinical study was conducted in 223 adult patients. At 12 months, all patients showed continuing symptomatic improvement as measured by the 18-item total ADHD symptom score.

INDICATIONS AND CLINICAL USE

ADDERALL XR (mixed salts amphetamine extended-release capsules) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive and/or inattentive symptoms that caused impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment (e.g. in social, academic, or occupational functioning), and must 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. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD 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. Drug treatment is 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 in patients with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of ADDERALL XR for long-term use, i.e., for more than 3 weeks in children aged 6 to 12 years and 4 weeks in adolescents aged 13 to 17 years, 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 (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, allergy to amphetamines or to components of ADDERALL XR (mixed salts amphetamine extended-release capsules) or its container.

Agitated states.

Patients with a history of drug abuse.

Administration of ADDERALL XR during or within 14 days following the administration of monoamine oxidase inhibitors may result in hypertensive crises (see Drug Interaction Section).

WARNINGS

Misuse and Serious Cardiovascular Adverse Events

Amphetamines have a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses that physicians should consider when prescribing this product.

The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems and Sudden Death

Children / Adolescents: Sudden death has been reported with sympathomimetic drugs used for ADHD treatment at therapeutic doses in children/adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, ADDERALL XR (mixed salts amphetamine extended-release capsules) generally should not be used in children / adolescents with known serious structural cardiac abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs (see CONTRAINDICATIONS)

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).

Hypertension and other Cardiovascular Conditions

Sympathomimetic medications can cause a modest increase in average blood pressure and average heart rate 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 WARNINGS and CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR (mixed salts amphetamine extended-release capsules), especially patients with hypertension.

General

Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other sympathomimetic drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who

develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Long-Term Suppression of Growth

In a controlled trial of ADDERALL XR in adolescents aged 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was –1.1lbs. and –2.8lbs., respectively, for patients receiving 10mg and 20mg ADDERALL XR. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

Published data for other stimulants report that in children aged 7-10 years, there is a temporary slowing in growth rate without evidence of growth rebound on treatment. Data are inadequate to determine whether the chronic use of amphetamines, in children may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Pre-existing Psychosis

Clinical experience suggests that in psychotic patients, administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children without a prior history of psychotic illness or mania can be caused by stimulants at therapeutic doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate (see CONTRAINDICATIONS).

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a 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.

Aggression

Aggressive behavior or hostility is often observed in children 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.

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 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, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment (see CONTRAINDICATIONS).

PRECAUTIONS

General

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.

Tics

Amphetamines have been reported to exacerbate motor and phonic tics in Tourette's syndrome. Therefore, careful clinical evaluation for tics in Tourette's syndrome in children and their families should precede use of stimulant medications. ADDERALL XR has been associated with new onset of tics (not necessarily associated with Tourette's syndrome).

Pregnancy / Teratogenic Effect

Amphetamine, in the enantiomer ratio present in ADDERALL XR (*d*- to *l*- ratio of 3:1), had no apparent effect on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses up to 6 and 16mg/kg/day, respectively. These doses are approximately 1.5 and 8 times the maximum recommended human dose of 30mg/day on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50mg/kg/day (approximately 6 times the maximum recommended human dose of 30mg/day on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

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 in children, 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 with ADDERALL XR in pregnant women. There has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took *d*-amphetamine sulfate with lovastatin during the first trimester of pregnancy.

Pregnancy / Non-teratogenic 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.

Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

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

Use in Geriatrics

ADDERALL XR has not been studied in the geriatric population.

Use in Pediatrics

ADDERALL XR is indicated for use in children 6 years of age and older. The long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children with ADHD under 6 years of age.

Carcinogenesis / Mutagenesis and 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 30mg/kg/day in male mice, 19mg/kg/day in female mice, and 5mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended-human dose of 30mg/day on a mg/m² 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 20mg/kg/day (approximately 5 times the maximum recommended human dose of 30mg/day on a mg/m² body surface area basis).

Dependence Liability

ADDERALL XR is a Schedule III drug under the Controlled Drugs and Substances Act (CDSA).

Amphetamines have been extensively abused (see WARNINGS). 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. Careful supervision is therefore recommended during drug withdrawal. 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.

Drug Interactions

Acidifying agents. Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) may lower absorption of amphetamines.

Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) 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.

Adrenergic blockers. As expected by their pharmacologic action, adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents. Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.), may increase absorption of amphetamines. Coadministration 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.

Proton Pump Inhibitors. Proton Pump Inhibitors act on proton pumps by blocking acid production thereby reducing gastric acidity. In the presence of a proton pump inhibitor, the median T_{max} of ADDERALL XR was shortened from 5 hours to 2.75 hours. Therefore, co-administration of ADDERALL XR and proton pump inhibitors should be avoided.

Antidepressants, tricyclic. Amphetamines may enhance the activity of tricyclic antidepressant 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.

MAO inhibitors. Monoamine oxidase inhibitor antidepressants, as well as a metabolite of furazolidone, 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 neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines. Amphetamines may counteract the sedative effect of some antihistamines.

Antihypertensives. Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine. Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide. Amphetamines may delay intestinal absorption of ethosuximide.

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.

Meperidine. Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy. Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine. Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital. Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin. Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

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

Veratrum alkaloids. Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Laboratory Tests

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

ADVERSE REACTIONS

In a single-dose pharmacokinetic study in 23 adolescents aged 13 to 17 years, 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 10mg and 20mg 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.

The pre-marketing development program for ADDERALL XR (mixed salts amphetamine extended-release capsules) included exposures in a total of 1315 participants in clinical trials (635 pediatric patients aged 6 to 12 years, 350 adolescent patients aged 13-17 years, 248 adult patients, 82 healthy adult subjects). The 635 pediatric patients were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (n=40). The 248 adult patients were evaluated in one controlled clinical study and one open-label clinical study. The 350 adolescent patients were evaluated in one controlled clinical study and one pharmacokinetic study. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse Events Associated with Discontinuation of Treatment

In two placebo-controlled studies of up to 5 weeks duration in children aged 6 to 12 years with ADHD, 2.4% (10/425) of ADDERALL XR treated patients discontinued due to adverse events (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 events associated with discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (n=595) are presented below. Over half of these patients were exposed to ADDERALL XR for 12 months or more.

Table 1: Most Frequent Adverse Events Resulting in Discontinuation (>0.5%)

Adverse Event	% of Pediatric Patients Discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight Loss	1.2
Emotional Lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents aged 13 to 17 years with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among ADDERALL XR-treated patients (n=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.

In one placebo-controlled, 4-week study in adults with ADHD, the most frequent adverse events resulting in discontinuation (>0.5%) in ADDERALL XR treated patients (n=191) were for nervousness including anxiety and irritability (3.1%); for insomnia (2.6%); and for headache, palpitation, and somnolence (1% each). In an open-label extension of the trial (n=223), at 12 months, the only adverse event leading to discontinuation that was reported by at least 2% of patients was depression (4.9%).

Adverse events leading to discontinuations for ADDERALL XR trials in adults were consistent with those reported in ADDERALL XR trials in children and were also consistent with the known side effects for amphetamines.

Adverse Events Occurring in a Controlled Trial

Adverse events reported in a controlled fixed-dose clinical study of pediatric patients treated with ADDERALL XR at doses up to 30 mg/day, or placebo, for up to 3 weeks are presented in the following table.

Table 2: Adverse Events Reported by More than 1% of Children aged 6 to 12 years Receiving Fixed Doses of ADDERALL XR (up to final doses of 10, 20 or 30mg/day) with an Incidence Greater than Placebo in a Controlled Clinical Study

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

Adverse events reported in a 4-week clinical trial in adolescents aged 13 to 17 years treated with ADDERALL XR at doses up to 40mg/day in adolescents weighing $\leq 75\text{kg}/165\text{lbs}$, or placebo are presented in the following table.

Table 3: Adverse Events Reported by $\geq 1\%$ * or more of Adolescents Weighing $\leq 75\text{kg}/165\text{lbs}$ Receiving ADDERALL XR with Higher Incidence than Placebo in a Forced Weekly-Dose Titration Study*

Body System	Adverse Event	ADDERALL XR (n=233)	Placebo (n=54)
General	Abdominal pain (stomach ache)	11%	2%
	Asthenia	3%	0%
Cardiovascular	Tachycardia	1%	0%
Digestive	Loss of Appetite ^a	36%	2%
	Dry Mouth	4%	0%
	Dyspepsia	3%	0%
	Nausea	3%	0%
	Vomiting	3%	0%
	Diarrhea	2%	0%
Nervous	Insomnia ^a	12%	4%
	Nervousness	6%	6% ^b
	Somnolence	5%	4%
	Emotional Lability	3%	0%
	Depression	1%	0%
	Twitching	1%	0%
Metabolic/Nutritional	Weight Loss ^a	9%	0%
Skin and Appendages	Herpes Simplex	1%	0%
Urogenital	Albuminuria	2%	0%
	Dysmenorrhea	1%	0%

^a Dose-related adverse events ^b Appears the same due to rounding

* Included doses up to 40mg

Adverse events reported in a controlled fixed dose clinical study of adult patients treated with ADDERALL XR at doses up to 60mg/day, or placebo, for up to 4 weeks are presented in the following table.

Table 4: Adverse Events Reported by $\geq 1\%$ or More of Adults Receiving Fixed Doses of ADDERALL XR (up to final doses of 20, 40 or 60mg/day) with an Incidence Greater than Placebo in a Controlled Clinical Trial

Body System	Adverse Event	ADDERALL XR (n=191)	Placebo (n=64)
General	Headache	26%	13%
	Asthenia	6%	5%
	Pain	5%	5% ^a
	Infection	4%	2%
	Photosensitivity Reaction	3%	0%
	Chills	2%	0%
	Fungal Infection	2%	0%
	Neck Pain	2%	0%
Digestive System	Dry Mouth	35%	5%
	Loss of Appetite	33%	3%
	Nausea	8%	3%
	Diarrhea	6%	0%
	Constipation	4%	0%
	Tooth Disorder	3%	2%
	Gastroenteritis	1%	0%
	Thirst	1%	0%
Nervous System	Vomiting	1%	0%
	Insomnia	27%	13%
	Nervousness	13%	13% ^a
	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Hyperkinesia	4%	3%
	Libido Decreased	4%	0%
	Emotional Lability	3%	2%
	Somnolence	3%	2%
	Speech Disorder	2%	0%
	Amnesia	1%	0%
Cardiovascular System	Depersonalization	1%	0%
	Libido Increased	1%	0%
	Tachycardia	6%	3%
	Palpitation	4%	0%
Metabolic/ Nutritional	Hypertension	2%	0%
	Vasodilation	1%	0%
	Weight Loss	11%	0%
	Bilirubinemia	1%	0%
	SGOT Increased	1%	0%
	SGPT Increased	1%	0%

Body System	Adverse Event	ADDERALL XR (n=191)	Placebo (n=64)
Musculoskeletal	Twitching	3%	0%
	Myalgia	2%	2% ^a
	Arthralgia	1%	0%
Respiratory	Dyspnea	3%	0%
	Cough Increased	1%	0%
	Sinusitis	1%	0%
Skin and Appendages	Sweating	3%	0%
	Rash	2%	0%
Special Senses	Taste Perversion	2%	0%
Urogenital System	Urinary Tract Infection	5%	0%
	Dysmenorrhea	2%	0%
	Impotence	2%	0%
	Oliguria	1%	0%
	Urinary Tract Disorder	1%	0%
	Urination Impaired	1%	0%

^a Appears the same due to rounding

The following adverse reactions have also been associated with the use of amphetamine, or mixed salt amphetamines:

Cardiovascular System: elevation of blood pressure, sudden death, myocardial infarction, stroke, palpitations, tachycardia; there have been isolated reports of cardiomyopathy associated with chronic amphetamine use

Digestive System: anorexia, constipation, diarrhea, dryness of the mouth, unpleasant taste, other gastrointestinal disturbances

Eye Disorders: mydriasis, vision blurred

Metabolic and Nutritional: weight loss

Nervous System: aggressive behavior, anger, depression, dermatillomania, dizziness, dyskinesia, dysphoria, euphoria, headache, hostility, insomnia, irritability, change in libido, logorrhea, overstimulation, psychotic and manic episodes at recommended doses (e.g., hallucinations, delusional thinking, and mania), restlessness, tremor, new onset of tics or exacerbation of phonic and motor tics and Tourette's syndrome, seizures

Skin and Appendages: alopecia, hypersensitivity reactions including angioedema and anaphylaxis, urticaria, rash. Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported

Urogenital System: impotence

SYMPTOMS AND TREATMENT OF 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: Treatment of overdosage consists of appropriate supportive measures. Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit its recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

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

Animal Toxicology

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ADDERALL XR (mixed salts amphetamine extended-release capsules) is a once-a-day capsule administered orally in the morning. ADDERALL XR dosage should be individualized according to the needs and response of the patient.

ADDERALL XR should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted, to the lowest effective dosage, since individual patient response to ADDERALL XR varies widely.

ADDERALL XR should not be used in patients with symptomatic cardiovascular disease including coronary artery disease in adults and should generally not be used in patients with known serious structural cardiac

abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs (see CONTRAINDICATIONS and WARNINGS).

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other sympathomimetic drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Patients who are considered to need extended treatment with ADDERALL XR should undergo periodic evaluation of their cardiovascular status (see WARNINGS).

ADDERALL XR is a once-a-day capsule for the treatment of ADHD containing immediate-release and delayed-release pellets. Capsules may be taken whole in the morning, or the capsule may be opened and the entire contents sprinkled on applesauce. If using the sprinkle administration method, the sprinkled applesauce should be consumed immediately and not stored. Patients should eat the applesauce with sprinkled beads in its entirety and refrain from chewing. The dose of a single capsule should not be divided - the contents of the entire capsule should be taken. Afternoon doses should be avoided because of the long-acting nature of the drug, including the potential for insomnia.

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

Children (6 to 12 years of age)

Amphetamines are not recommended for children under 6 years of age: When in the judgement of the clinician a lower dose is appropriate, patients may begin treatment with 5mg once daily in the morning. The usual starting dose is 10mg daily. The daily dosage may be adjusted in increments of 5mg to 10mg at weekly intervals, as determined by clinical response and tolerability up to the maximum recommended dose of 30mg per day.

Adolescents (13 to 17 years of age) and Adults (over 18 years of age)

In adolescents and adults with ADHD who are either starting treatment for the first time or switching from another stimulant medication, start with 10mg once daily in the morning; daily dosage may be adjusted in increments of 5 to 10mg at weekly intervals up to a usual maximum of 20mg. In some cases, higher doses not to exceed 30mg/day may be required, as determined by clinical response and tolerability.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names:

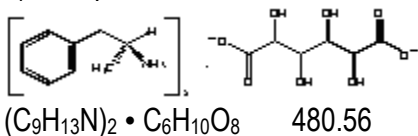
1. *d*-amphetamine Saccharate
2. Amphetamine Aspartate Monohydrate
3. *d*-amphetamine Sulfate USP
4. Amphetamine Sulfate USP

Chemical Names:

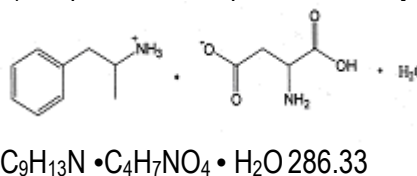
1. (+)- α -Methylphenethylamine saccharate (2:1)
2. (\pm)- α -Methylphenethylamine aspartate monohydrate
3. (+)- α -Methylphenethylamine sulfate (2:1)
4. (\pm)- α -Methylphenethylamine sulfate (2:1)

Structural Formula and Molecular Weights:

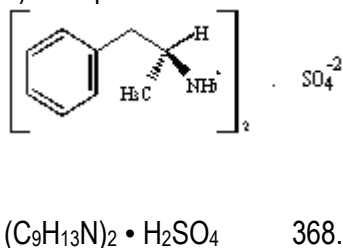
1) *d*-amphetamine Saccharate



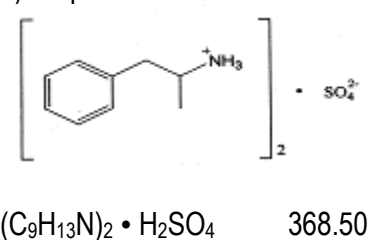
2) Amphetamine Aspartate Monohydrate



3) *d*-amphetamine Sulfate



4) Amphetamine Sulfate



Description: The four amphetamine salts are white to off-white, crystalline powder. The amphetamine sulfate is freely soluble in water while *d*-amphetamine sulfate, amphetamine aspartate and *d*-amphetamine saccharate are soluble in water. Also, the amphetamine salts are known to be stable molecules.

Composition

ADDERALL XR (mixed salts amphetamine extended-release capsules) is a long-acting, modified-release, single-entity amphetamine product designed for once-daily administration combining the neutral sulfate salts of *d*-amphetamine and amphetamine, with the *d*-isomer of amphetamine saccharate and *d,l*-amphetamine aspartate. The ADDERALL XR capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which provides for its prolonged duration of action.

<u>Each capsule contains:</u>	<u>5mg</u>	<u>10mg</u>	<u>15mg</u>	<u>20mg</u>	<u>25mg</u>	<u>30mg</u>
<i>d</i> -amphetamine Saccharate	1.25	2.5	3.75	5.0	6.25	7.5
Amphetamine Aspartate Monohydrate	1.25	2.5	3.75	5.0	6.25	7.5
<i>d</i> -amphetamine Sulfate USP	1.25	2.5	3.75	5.0	6.25	7.5
Amphetamine Sulfate USP	1.25	2.5	3.75	5.0	6.25	7.5
Total amphetamine base equivalence	1.5	3.0	4.5	6.0	7.5	9.0
Total <i>d</i> -amphetamine base equivalent	1.6	3.3	4.9	6.5	8.1	9.8

Inactive Ingredients and Colors: The inactive ingredients in ADDERALL XR capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, starch, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide.

The 5mg, 10mg and 15mg capsules also contain FD&C Blue #2. The 20mg, 25mg and 30mg capsules also contain red iron oxide and yellow iron oxide.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

ADDERALL XR 5mg Capsules: Clear/blue, imprinted "ADDERALL XR" on one end and "5 mg" on the other. Bottles of 100.

ADDERALL XR 10mg Capsules: Blue/blue, imprinted "ADDERALL XR" on one end and "10mg" on the other. Bottles of 100.

ADDERALL XR 15mg Capsules: Blue/white, imprinted "ADDERALL XR" on one end and "15mg" on the other. Bottles of 100.

ADDERALL XR 20mg Capsules: Orange/orange, imprinted "ADDERALL XR" on one end and "20mg" on the other. Bottles of 100.

ADDERALL XR 25mg Capsules: Orange/white, imprinted "ADDERALL XR" on one end and "25mg" on the other. Bottles of 100.

ADDERALL XR 30mg Capsules: Clear/orange, imprinted "ADDERALL XR" on one end and "30mg" on the other. Bottles of 100.

INFORMATION FOR THE CONSUMER

ADDERALL XR®*

mixed salts amphetamine
extended-release capsules
5mg, 10mg, 15mg, 20mg, 25mg and 30mg

INFORMATION FOR PATIENTS TAKING ADDERALL XR OR FOR THEIR PARENT OR CAREGIVER

Please read this before you start taking / giving ADDERALL XR. It may answer some of the questions you have and help you to understand how to take/give ADDERALL XR to obtain the best results. However, this leaflet does not contain all available information about ADDERALL XR and does not take the place of your / your child's doctor's instructions. If you need more information or advice about ADDERALL XR, talk to your / your child's doctor or pharmacist.

The following have been reported with use of ADDERALL XR and other sympathomimetic medicines.

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 has any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor may wish to check you or your child carefully for heart problems before starting ADDERALL XR. Your doctor may wish to 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.

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 Adolescents

- 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 while taking ADDERALL XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What is ADDERALL XR?

ADDERALL XR is a once-a-day treatment for Attention Deficit Hyperactivity Disorder (ADHD). ADDERALL XR capsules contain a combination of amphetamines, the active ingredient in the treatment of ADHD.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not organized, losing things, forgetful, not following directions and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms. Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least six months to be certain of the diagnosis.

How does ADDERALL XR work?

Amphetamines, the active ingredient in ADDERALL XR, help increase attention (including the ability to follow directions and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD. The ADDERALL XR capsule contains some beads that release medication immediately giving you / your child an initial dose of medication, and other delayed-release beads which release medication later during the day to keep improving the symptoms of ADHD throughout the day and into the early evening.

When ADDERALL XR should not be used

You / your child should NOT take ADDERALL XR if one or more of the following applies to you / your child:

- allergies to amphetamines or any of the other ingredients in ADDERALL XR
- advanced arteriosclerosis (hardened arteries)
- symptomatic cardiovascular disease
- moderate to severe high blood pressure
- agitated states
- glaucoma, an eye disease
- hyperthyroidism (an overactive thyroid gland)
- history of drug abuse
- has taken medications from the group called monoamine oxidase inhibitors (MAOI) within the last 14 days.

Before using ADDERALL XR

Use of ADDERALL XR may be unsuitable or require special attention under certain medical conditions. Tell the doctor if one or more of the following applies to you/ your child:

- heart disease or condition structural heart abnormalities, or high blood pressure
- family history of sudden death or death related to heart problems
- does strenuous exercise
- takes other drugs for ADHD
- has abnormal thoughts or visions, hears abnormal sounds or voices, or has been diagnosed with psychosis presently or in the past
- has symptoms of depression (feelings of sadness, worthlessness or hopelessness) or bipolar disorder (mood swings), or has been diagnosed with depression or bipolar disorder presently or in the past
- family history of suicide, depression, or bipolar disorder
- has motion tics (hard to control, repeat twitching of any parts of the body) or verbal tics (hard to control repeating of sounds or words) or Tourette's syndrome
- has relatives with motion tics, verbal tics, or Tourette's syndrome
- pregnancy or plans to become pregnant
- breastfeeding or plans to breastfeed
- has a history of seizures (convulsions, epilepsy)

Tell the doctor if you / your child develops any of the above conditions or symptoms while taking ADDERALL XR.

How should ADDERALL XR be taken?

ADDERALL XR should be taken by mouth, once a day early in the morning.

Capsules may be swallowed whole with water or milk. Capsules may be opened and all the beads inside sprinkled on applesauce and taken immediately; do not store for later use. **Do not crush or chew the capsule or the beads before swallowing.** ADDERALL XR can be taken with or without meals.

Do not take antacids at the same time as ADDERALL XR.

ADDERALL XR may interact with a class of medications that reduce the acid produced in the stomach called Proton Pump Inhibitors, commonly known as PPI (e.g., Losec®).

In order to receive the most benefit from ADDERALL XR, it is important that ADDERALL XR be taken only as directed by your / your child's doctor. The doctor may adjust the amount of drug taken by you / your child until it is right for you / your child. From time to time, the doctor may interrupt treatment to check your / your child's symptoms while you / your child is not taking the drug.

What are the possible side effects of ADDERALL XR?

Along with its desired effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, talk to your / your child's doctor.

During clinical studies with ADDERALL XR, the most common side effects in children aged 6 to 12 years were decreased appetite, stomach ache, difficulty falling asleep and mood swings; in adolescents aged 13 to 17 years were stomach ache, loss of appetite, difficulty falling asleep and weight loss; and in adults were dry mouth, decreased appetite, headache, difficulty falling asleep, and weight loss. This is not a complete list of possible side effects. Ask your / your child's doctor about other possible side effects.

Can ADDERALL XR be taken with other medications?

It is important to tell your / your child's doctor or pharmacist about all medicines that you / your child is taking including other medicines that a doctor has prescribed, medicines that you buy yourself without a prescription, and any herbal remedies that you / your child is taking.

Do not take antacids at the same time as ADDERALL XR.

ADDERALL XR may interact with a class of medications that reduce the acid produced in the stomach called Proton Pump Inhibitors, commonly known as PPI (e.g., Losec®).

While on ADDERALL XR, do not start taking a new medicine or herbal remedy before checking with the doctor.

Other important safety information:

Abuse of amphetamines can lead to dependence and possibly serious heart problems and death. Substance abuse may be less likely in patients with ADHD if they are treated with medication. ADDERALL XR should only be given under close medical supervision to patients whose condition has been properly diagnosed.

Sudden death has been reported with drugs used for ADHD treatment in children/adolescents with structural heart abnormalities or other serious heart problems. Although some serious heart problems alone can carry an increased risk of sudden death, ADDERALL XR generally should not be used in children, adolescents or adults with known structural heart abnormalities, disease of the heart muscle, serious heart rhythm abnormalities or other serious heart disease or conditions.

Other stimulants have been reported to temporarily slow growth in children, however there is not sufficient evidence to determine if ADDERALL XR in children may cause slower growth (slowed weight gain and/or height). The doctor will be carefully watching your / your child's height and weight. If you / your child is not growing or gaining weight as the doctor expects, the doctor may stop the patient's ADDERALL XR treatment.

Call the doctor **immediately** if you / your child takes more than the amount of ADDERALL XR prescribed by the doctor.

What else should I know about ADDERALL XR?

ADDERALL XR has not been studied in children under six years of age. ADDERALL XR has not been studied in pregnant women.

ADDERALL XR may be a part of the patient's overall treatment for ADHD. The doctor may also recommend that you / your child have counseling or other therapy.

As with all medicines, never share ADDERALL XR with anyone else and take only the number of ADDERALL XR capsules prescribed by your / your child's doctor.

Storage**Keep out of the reach of children.**

Store ADDERALL XR at 25°C (excursions permitted to 15 -30°C) in a tight, light-resistant container.

* ADDERALL XR is a registered trade-mark used under licence from Shire US Inc.

PHARMACOLOGY

The behavioral manifestations of ADHD are believed to involve an interactive imbalance between dopaminergic and other neurotransmitter systems. However, a fundamental dopaminergic dysfunction appears to have special significance. Amphetamine increases the availability of synaptic dopamine at key sites in the brain by stimulating its release from newly synthesized (cytoplasmic) dopamine pools. Thus, unlike methylphenidate, which increases dopamine availability primarily by blocking reuptake, amphetamine's effect does not appear to be highly dependent on impulse-released dopamine.

This primary mechanism of action of amphetamine is supported by experiments with reserpine and α -methyltyrosine. Pretreatment with reserpine, which is believed to reduce stored vesicular (but not cytoplasmic) dopamine, was ineffective in attenuating responses to amphetamine challenge. In contrast, the depletion of newly synthesized cytoplasmic dopamine through the inhibition of tyrosine hydroxylase (the rate limiting anabolic enzyme) using α -methyltyrosine, did reduce responses following amphetamine challenge.

Systemically administered amphetamine produced stimulation of dopamine release from the nucleus accumbens and dorsal caudate. Administration of a low acute dose of amphetamine produced a region specific decrease in dopamine from the "shell" in comparison to the "core" regions of the nucleus accumbens. Higher acute doses increased extracellular dopamine to the same extent in both regions.

In addition to a dopaminergic mechanism of action, there is experimental evidence to suggest involvement of other neurotransmitter systems in the regulation of behavioral effects (e.g., motor activity). These include interactions between dopaminergic, GABAergic and glutamatergic pathways and possible involvement of cholinergic pathways.

Amphetamine-induced effects are primarily mediated by D₁ and D₂ receptors. In addition, 5-HT_{2A} and 5-HT₃ receptors, and NMDA receptors are suggested to play a role in amphetamine-induced release of dopamine, and in the regulation of the firing rate and pattern of midbrain dopamine neurons, respectively.

Prenatal exposure to amphetamine was associated with a variety of responses in offspring that included increases in conditioned avoidance, exploratory behavior, and sexual behavior, and decreases in 5-HT content in the medial hypothalamus.

Repeated administration of high concentrations of amphetamine produced striatal, neostriatum, and frontal cortex dopamine nerve fiber degeneration.

Amphetamine interacted with a variety of compounds that included caffeine, cocaine, morphine, diazepam, phencyclidine, clonidine, fluoxetine, lithium, pentobarbital, ethanol, and THC. The mechanism of many of these interactions is currently not known.

Animal Pharmacokinetics

ADDERALL XR (mixed salts amphetamine extended-release capsules) is a once a day product containing immediate-release and delayed-release pellets that has been shown to provide a double-pulsed delivery of amphetamine in patients with ADHD.

Literature studies indicated a stereospecific distribution of the individual dextro (*d*-) and levo (*l*-) enantiomers of amphetamine in the brain and heart of mice. Distribution kinetics in the rat indicated that similar amounts of both enantiomers were excreted in the urine as parent drug and as the hydroxy metabolite.

Radiolabelled ³H-*d*-amphetamine was distributed in many tissues of pregnant and non-pregnant females and male mice. Amphetamine crossed the placenta and was present in the placenta, whole fetus, and in fetal brain and liver. Fetal tissue concentrations were generally much lower than maternal tissue concentrations.

The metabolism of amphetamine was affected by induction of the CYP450 system with phenobarbital. The direct benzene ring hydroxylation of parent drug was mediated by CYP2D1 in the rat and by the human homologue, CYP2D6, in human microsomes. The deamination of amphetamine was shown to be mediated by the CYP isoform 2C3 from the rabbit, but not the 2C11 and 2C13 isoforms from the rat. N-oxygenation of amphetamine to the hydroxylamine and oxime metabolites was demonstrated in vitro with flavin containing monooxygenase Form 3 from humans.

The urinary excretion of amphetamine and its major rat metabolite, 4-hydroxyamphetamine, was influenced by strain of rat, significant differences occurring between poor metabolizer versus extensive metabolizer strains.

Human Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR (mixed salts amphetamine extended-release capsules) have been conducted in healthy adult and pediatric (aged 6-12 years) subjects, and adolescent (aged 13-17 years) and pediatric patients with ADHD. ADDERALL XR capsules contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1.

ADDERALL XR demonstrates linear pharmacokinetics over the dose range of 20 to 60mg in adults and adolescents aged 13 to 17 years weighing greater than 75kg/165lbs, over the dose range of 10 to 40mg in adolescents weighing less than or equal to 75kg/165lbs, and 5 to 30mg in children aged 6 to 12 years. There was no unexpected accumulation at steady state in children.

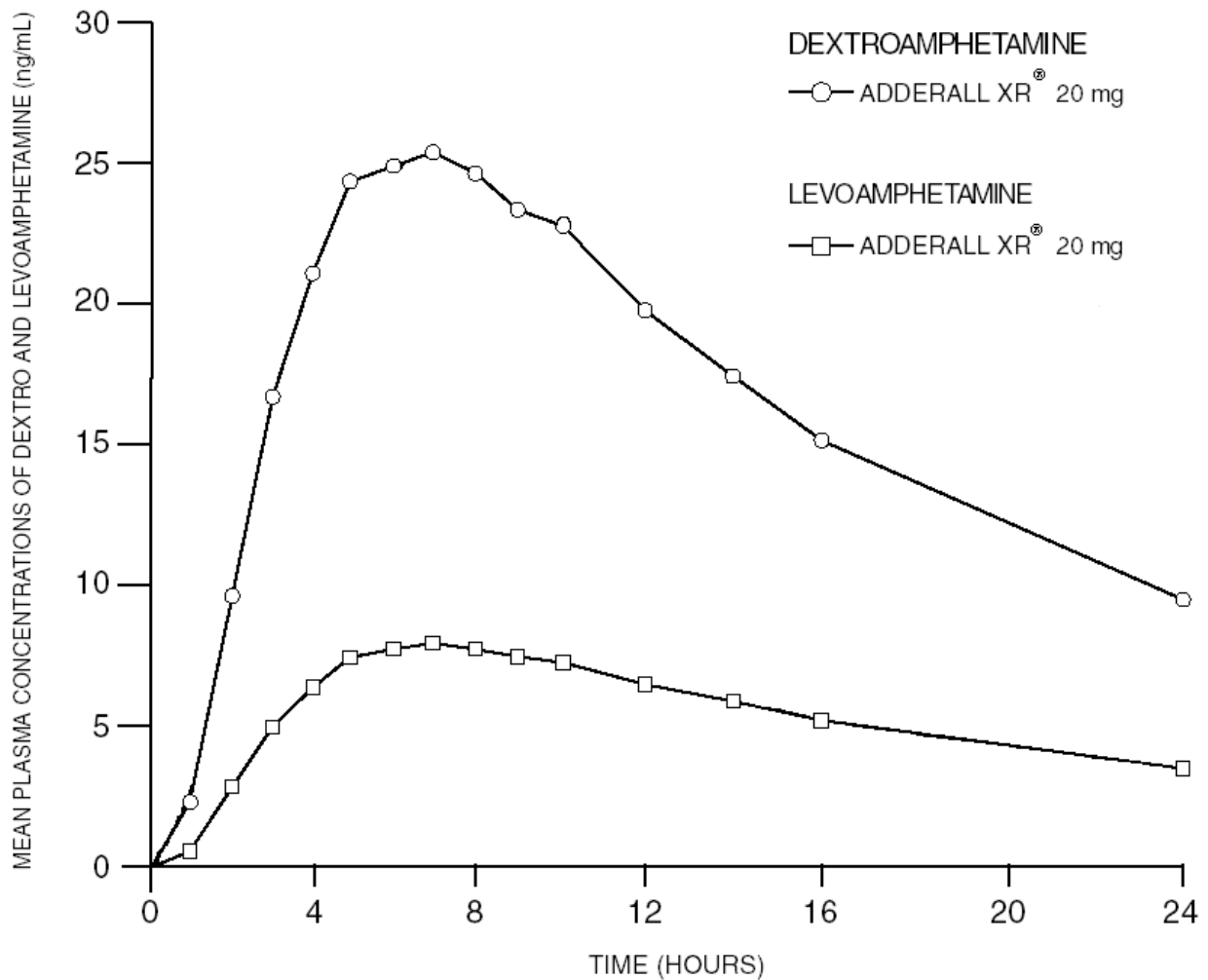
Pharmacokinetic Results in Healthy Adult and Pediatric Subjects

Following administration of a single dose of ADDERALL XR in healthy adult subjects, the peak plasma concentrations occurred in about 7 hours for *d*-amphetamine and 8 hours for *l*-amphetamine as seen in Table 5.

Table 5: Pharmacokinetic Parameters for Single 20 mg Dose of ADDERALL XR

Treatment	<i>d</i> -amphetamine			<i>l</i> -amphetamine		
	AUC _{0-inf} (ng•hr/mL)	T _{max} (hours)	C _{max} (ng/mL)	AUC _{0-inf} (ng•hr/mL)	T _{max} (hours)	C _{max} (ng/mL)
ADDERALL XR (20mg, qd)	567	7.0	28.1	203	8.2	8.7

Figure 1: Mean *d*-amphetamine and *l*-amphetamine Plasma Concentrations following a single 20 mg morning Administration of ADDERALL XR in the Fed State.



The mean elimination half-life is 1 hour shorter for *d*-amphetamine and 2 hours shorter for *l*-amphetamine in children aged 6 to 12 years compared to that in adults ($t_{1/2}$ is 10 hours for *d*-amphetamine and 13 hours for *l*-amphetamine in adults, and 9 hours and 11 hours, respectively, for children).

Pharmacokinetic Results in Children and Adolescents with ADHD

In a 20mg single dose study in 51 children (aged 6-12 years) with ADHD, the mean T_{max} for *d*-amphetamine was 6.8 hours and the mean C_{max} was 48.8ng/mL. The corresponding mean T_{max} and C_{max} values for *l*-amphetamine were 6.9 hours and 14.8ng/mL, respectively. The mean elimination half-life for *d*-amphetamine and *l*-amphetamine was 9.5 and 10.9 hours, respectively. Following dosing of children with ADHD to steady state with ADDERALL XR 10, 20 and 30mg the mean *d*-amphetamine C_{max} (ng/mL) in plasma for ADDERALL XR was 28.8 (10mg), 54.6 (20mg) and 89.0 (30mg). For *l*-amphetamine, the mean C_{max} values for the three ADDERALL XR doses were 8.8, 17.2 and 28.1ng/mL, respectively.

In adolescents aged 13-17 years and weighing less than or equal to 75kg/165lbs, the mean elimination half-life for *d*-amphetamine is 11 hours, and 13-14 hours for *l*-amphetamine.

Table 6: ADDERALL XR Pharmacokinetic Parameters at Steady State in Children with ADHD

Treatment	<i>d</i> -amphetamine			<i>l</i> -amphetamine		
	AUC ₀₋₂₄ (ng•hr/mL)	T _{max} (hours)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng•hr/mL)	T _{max} (hours)	C _{max} (ng/mL)
ADDERALL XR (10mg)	432	6.4	28.8	138	6.4	8.8
ADDERALL XR (20mg)	777	5.8	54.6	262	5.7	17.2
ADDERALL XR (30mg)	1364	5.5	89.0	444	5.5	28.1

Metabolism

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.

Excretion

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 PRECAUTIONS – Drug Interactions).

Bioequivalence of 1 x 20mg Capsule to 4 x 5mg Capsules

Children with ADHD

In a single dose study in 20 children (aged 6-12 years) with ADHD, a single administration of four 5mg capsules of ADDERALL XR was shown to be bioequivalent to a single 20mg capsule for both *d*- and *l*-amphetamine under fasting conditions.

Table 7: Pharmacokinetic Parameters for ADDERALL XR

Summary Table of the Comparative Bioavailability Data ADDERALL XR 4 x 5mg Capsules vs 1 x 20mg Capsule - Under Fasting Conditions From Measured Data				
Parameter	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geo- metric Means	Confidence Interval (90% CI)
	ADDERALL XR 4x5mg capsules	ADDERALL XR 1x20mg capsules		
<i>d</i>-amphetamine				
AUC _T (ng•h/mL)	823.5 843.5 (22.2%)	775.7 794.8 (22.6%)	106.2	101.0 -111.6
AUC _I (ng•h/mL)	845.8 863.9 (21.1%)	797.8 815.3 (21.4%)	106.0	101.5 - 110.7
C _{max} (ng/mL)	50.4 51.9 (24.5%)	49.9 51.9 (28.9%)	101.0	92.4 -110.3
T _{max} * (h)	4.65 (50.0%)	4.50 (37.8%)		
T _{1/2} * (h)	8.10 (14.5%)	7.98 (17.0%)		
<i>l</i>-amphetamine				
AUC _T (ng•h/mL)	276.8 286.2 (26.4%)	238.5 247.0 (27.1%)	116.0	108.6 -124.0
AUC _I (ng•h/mL)	297.1 304.0 (22.3%)	263.7 269.6 (21.7%)	112.7	107.6 -118.0
C _{max} (ng/mL)	16.2 16.7 (24.1%)	15.2 15.8 (28.6%)	106.6	98.5 -115.3
T _{max} * (h)	4.95 (50.1%)	4.85 (39.7%)		
T _{1/2} * (h)	9.16 (14.5%)	9.13 (18.5%)		

* Arithmetic mean (CV%)

For both *d*- and *l*-amphetamine, statistically significant differences were noted between the two treatment groups for AUC, with the 4 x 5mg group showing higher AUC, but not for C_{max} and T_{max}.

Food Effect Study in Healthy Adult Subjects

A single dose study compared the relative bioavailability of *d*-amphetamine and *l*-amphetamine following administration of a single 30mg dose of ADDERALL XR fasted, fed (high fat meal) and sprinkled on food (otherwise fasted) in 21 healthy adult subjects. Food does not affect the extent of absorption of ADDERALL XR capsules, but prolongs T_{max} by 2.5 hours by administration with food (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted states.

TOXICOLOGY

Acute Toxicity Studies

The acute LD₅₀ amphetamine is as follows:

<u>Species</u>	<u>LD₅₀ (mg/kg)</u>
Mice (i.v.)	52
Mice (oral)	353
Rat (i.p.)	70
Dog (i.v.)	8.5
Monkey (i.v., oral)	5

Acute toxicity studies conducted in mice, rats, dogs and monkeys showed similar dose-dependent responses. The order for comparative toxicity ranking, based upon the LD₅₀ values, was monkey>dog>mouse.

Acute toxicity to dextro (*d*-), and levo (*l*-) amphetamine was age-dependent. Young mice (3-30 days old) tolerated higher doses (up to 180mg/kg i.p.) than adults. Toxicity increased from 18-days of age onward. Mortality response curves were biphasic for developing mice and polyphasic for adult mice.

Acute toxicity signs noted in mice (25-75mg/kg i.v.), rats (45-178mg/kg i.p.), dogs (5-9mg/kg i.v.) and monkeys (1-6mg/kg i.v.) included marked to severe hyperactivity, stereotypic behavior, mild to marked clonic and/or tonic convulsions, and (in monkeys) marked increase in respiratory rate, body temperature and pupil size. Death was associated with convulsions and, in dogs, massive endocardial hemorrhages in both ventricles.

Subacute and Subchronic Toxicity Studies

Subacute and subchronic toxicity signs noted in mice (0-2000 ppm of *d,l*-amphetamine in feed) and rats (0-750 ppm of *d,l*-amphetamine in feed) from 14-day and 13-week dietary studies included hyperactivity, decreased body weight and food consumption. Deaths in the order of 15 to 65% were reported in mice administered with 500-2000 ppm of *d,l*-amphetamine in feed. No treatment-related deaths occurred in the rat study.

Carcinogenicity Studies

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 30mg/kg/day in male mice, 19mg/kg/day in female mice, and 5mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times respectively the maximum recommended human dose of 30mg/day on a mg/m² body surface area basis.

Reproduction and Teratology Studies

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 5 times the maximum recommended human dose of 30mg/day on a mg/m² body surface area basis). Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50mg/kg/day (approximately 6 times the maximum recommended human dose of 30mg/day on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d-d, l-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.

Mutagenicity Studies

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.

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