

**ADDERALL - dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate and amphetamine sulfate tablet**

Shire US Inc.

**AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.**

**DESCRIPTION**

A single-entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate monohydrate.

<b>EACH TABLET CONTAINS:</b>	<b>5 mg</b>	<b>7.5 mg</b>	<b>10 mg</b>	<b>12.5 mg</b>	<b>15 mg</b>	<b>20 mg</b>	<b>30 mg</b>
Dextroamphetamine Saccharate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	4.7 mg	6.3 mg	7.8 mg	9.4 mg	12.6 mg	18.8 mg

**Inactive Ingredients:** lactitol, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, and other ingredients.

**Colors:** ADDERALL<sup>®</sup> 5 mg is a white to off-white tablet, which contains no color additives.

ADDERALL<sup>®</sup> 7.5 mg and 10 mg contain FD & C Blue #1.

ADDERALL<sup>®</sup> 12.5 mg, 15 mg, 20 mg and 30 mg contain FD & C Yellow #6 as a color additive.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

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**

ADDERALL<sup>®</sup> tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30 mg of ADDERALL<sup>®</sup> to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-amphetamine. The mean elimination half-life ( $t_{1/2}$ ) for d-amphetamine was shorter than the  $t_{1/2}$  of the l-isomer (9.77-11 hours vs. 11.5-13.8 hours). The PK parameters ( $C_{max}$ ,  $AUC_{0-inf}$ ) of d- and l-amphetamine increased approximately three-fold from 10 mg to 30 mg indicating dose-proportional pharmacokinetics.

The effect of food on the bioavailability of ADDERALL<sup>®</sup> has not been studied.

**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  $\alpha$  or  $\beta$  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 PRECAUTIONS).

## INDICATIONS

ADDERALL<sup>®</sup> is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

### Attention Deficit Hyperactivity Disorder (ADHD)

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV<sup>®</sup>) 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 child and not solely on the presence of the required number of DSM-IV<sup>®</sup> characteristics.

### Need for Comprehensive Treatment Program

ADDERALL<sup>®</sup> 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 children with this syndrome. Stimulants are not intended for use in the child 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<sup>®</sup> for long-term use has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL<sup>®</sup> for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

## **WARNINGS**

### **Psychosis**

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

### **Long-Term Suppression of Growth**

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, 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 should have their treatment interrupted.

### **Sudden Death and Pre-existing Structural Cardiac Abnormalities**

Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. ADDERALL<sup>®</sup> generally should not be used in children or adults with structural cardiac abnormalities.

## **PRECAUTIONS**

### **General**

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

### **Hypertension**

Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS).

Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL<sup>®</sup>, especially patients with hypertension. Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication.

### **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 children and their families should precede use of stimulant medications.

### **Effects on Weight**

Amphetamines have been associated with decreased appetite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These reductions in expected weight attenuate over time and are greatest in the heaviest children.

### **Information for Patients**

Amphetamines 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.

### **Drug Interactions**

*Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) 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 blocker* -Adrenergic blockers are inhibited by amphetamines.

*Alkalinizing agents* -Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL<sup>®</sup> 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.

*Antidepressants, tricyclic* -Amphetamines may enhance the activity of tricyclic 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* -MAOI 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 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.

*Methamphetamine therapy* -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine 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 overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

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

### **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.

### **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 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m<sup>2</sup> body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL<sup>®</sup>(immediate-release)(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<sup>®</sup> (immediate-release)(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 30 mg/day on a mg/m<sup>2</sup> body surface area basis).

### **Pregnancy**

#### **Teratogenic Effects**

Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL<sup>®</sup>(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 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m<sup>2</sup> 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 6 times that of a human dose of 30 mg/day [child] on a mg/m<sup>2</sup> 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, 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.

Usage in Nursing Mothers

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

### **Pediatric Use**

Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Hyperactivity Disorder described under INDICATIONS AND USAGE.

### **Geriatric Use**

ADDERALL<sup>®</sup> has not been studied in the geriatric population.

## **ADVERSE REACTIONS**

### **Cardiovascular**

Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

### **Central Nervous System**

Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

### **Gastrointestinal**

Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

### **Allergic**

Urticaria, rash, rare reports of angioedema, rare reports of a symptom complex resembling anaphylaxis.

### **Endocrine**

Impotence, changes in libido.

## **DRUG ABUSE AND DEPENDENCE**

ADDERALL<sup>®</sup> is a Schedule II controlled substance.

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 include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

## **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 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. 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 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.

## DOSAGE AND ADMINISTRATION

Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted according to the therapeutic needs and response of the patient. Late evening doses should be avoided because of the resulting insomnia.

### Attention Deficit Hyperactivity Disorder

Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

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

### Narcolepsy

Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

## HOW SUPPLIED

ADDERALL<sup>®</sup> 5 mg: A round, flat-faced beveled edge, white to off-white tablet, "5" embossed on one side with partial bisect and "AD" embossed on the other side (NDC 54092-371-01)

ADDERALL<sup>®</sup> 7.5 mg: An oval, convex, blue tablet, "7.5" embossed on one side with a partial bisect and "AD" embossed on the other side with a full and partial bisect (NDC 54092-372-01)

ADDERALL<sup>®</sup> 10 mg: A round, convex, blue tablet, "10" embossed on one side with a full and partial bisect and "AD" embossed on the other side (NDC 54092-373-01)

ADDERALL<sup>®</sup> 12.5 mg: A round, flat-faced beveled edge, orange tablet, "12.5" embossed on one side and "AD" embossed on the other side with a full and partial bisect (NDC 54092-374-01)

ADDERALL<sup>®</sup> 15 mg: An oval, convex, orange tablet, "15" embossed on one side with a partial bisect and "AD" embossed on the other side with a full and partial bisect (NDC 54092-375-01)

ADDERALL<sup>®</sup> 20 mg: A round, convex, orange tablet, "20" embossed on one side with a full and partial bisect and "AD" embossed on the other side (NDC 54092-376-01)

ADDERALL<sup>®</sup> 30 mg: A round, flat-faced beveled edge, orange tablet, "30" embossed on one side with a full and partial bisect and "AD" embossed on the other side (NDC 54092-377-01)

In bottles of 100 tablets.

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

Store at 25°C (77°F), excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]

### Rx only.

### 002979

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Made in USA

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