

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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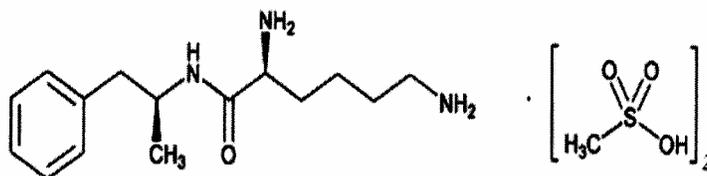
**APPROVED LABELING**

**AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. 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

Vyvanse (lisdexamfetamine dimesylate) is designed as a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate. The molecular formula is  $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$ , which corresponds to a molecular weight of 455.60. The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Vyvanse capsules contain 30 mg, 50 mg and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: D&C Red #28, D&C Yellow #10, FC&C Blue #1 and FD&C Red #40.

## CLINICAL PHARMACOLOGY

### Mechanism of Action and Pharmacology

Vyvanse is a pro-drug of dextroamphetamine. After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. 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. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

### **Pharmacokinetics**

Pharmacokinetic studies of dextroamphetamine after oral administration of lisdexamfetamine dimesylate have been conducted in healthy adult and pediatric (6–12 yrs) patients with ADHD.

In 18 pediatric patients (6–12 yrs) with ADHD, the T<sub>max</sub> of dextroamphetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate either 30 mg, 50 mg, or 70 mg after an 8-hour overnight fast. The T<sub>max</sub> of lisdexamfetamine dimesylate was approximately 1 hour. Linear pharmacokinetics of dextroamphetamine after single-dose oral administration of lisdexamfetamine dimesylate was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years.

There is no accumulation of dextroamphetamine AUC at steady state in healthy adults and no accumulation of lisdexamfetamine dimesylate after once-daily dosing for 7 consecutive days.

Food does not affect the observed AUC and C<sub>max</sub> of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of Vyvanse capsules but prolongs T<sub>max</sub> by approximately 1 hour (from 3.8 hrs at fasted state to 4.7 hrs after a high fat meal). After an 8-hour fast, the AUC for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Weight/Dose normalized AUC and C<sub>max</sub> were 22% and 12% lower, respectively, in adult females than in males on day 7 following a 70 mg/day dose of lisdexamfetamine for 7 days. Weight/Dose normalized AUC and C<sub>max</sub> values were the same in girls and boys following single doses of 30-70 mg.

### **Metabolism and Excretion**

After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine dimesylate is converted to dextroamphetamine and L-lysine, which is believed to occur by first-pass intestinal and/or hepatic metabolism. Lisdexamfetamine is not metabolized by cytochrome P450 enzymes. Following the oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine dimesylate are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers.

Dextroamphetamine is known to inhibit monoamine oxidase. The ability of dextroamphetamine 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, but there are no in vivo studies of p450 enzyme inhibition.

### Special Populations

The pharmacokinetics of dextroamphetamine is similar in pediatric (6-12 years) and adolescent (13-17 years) ADHD patients, and healthy adult volunteers. Any differences in kinetics seen after oral administration are a result of differences in mg/kg dosing.

### Gender

Systemic exposure to dextroamphetamine is similar for men and women given the same mg/kg dose.

### **Clinical Trials**

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6–12 (N=290) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of Vyvanse or placebo once daily in the morning for four weeks. Significant improvements in patient behavior, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at endpoint for all Vyvanse doses compared to patients who received placebo. Mean effects at all doses were fairly similar, although the highest dose (70 mg/day) was numerically superior to both lower doses (30 and 50 mg/day). The effects were maintained throughout the day based on parent ratings (Connor's Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm).

A double-blind, placebo-controlled, randomized, crossover design, analog classroom study was conducted in children aged 6-12 (N=52) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 3-week open-label dose titration with ADDERALL XR®, patients were randomly assigned to continue the same dose of ADDERALL XR® (10, 20, or 30 mg), Vyvanse (30, 50, and 70 mg), or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the Swanson, Kotkin, Agler, M.Flynn and Pelham (SKAMP)-Department scores across the 8 sessions of a 12 hour treatment day, was observed between patients who received Vyvanse compared to patients who received placebo. The drug effect was similar for all 8 sessions.

### **INDICATIONS AND USAGE**

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The efficacy of Vyvanse in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, who met DSM-IV® criteria for ADHD (see CLINICAL TRIALS).

A diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD; DSM-IV®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, in social, academic, or occupational functioning, and be present in two or more settings, e.g., at 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® characteristics.

**Need for Comprehensive Treatment Program:** Vyvanse 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 Vyvanse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Vyvanse 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**

### **Serious Cardiovascular Events**

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

##### Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

##### 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**

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

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

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

## **Psychiatric Adverse Events**

### **Pre-Existing Psychosis**

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

### **Bipolar Illness**

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

### **Emergence of New Psychotic or Manic Symptoms**

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

### **Aggression**

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

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

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d to l enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and 20 mg of amphetamine (d to l enantiomer ratio of 3:1). Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of lisdexamfetamine in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to a 1 lb weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received lisdexamfetamine over 12 months suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile of -13.4 over 1 year (average percentile at baseline and 12 months, were 60.6 and 47.2, respectively). Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

## **Seizures**

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizure, 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.

## **PRECAUTIONS**

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

**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.

**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.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with lisdexamfetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Vyvanse. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

### **Drug Interactions:**

*Urinary acidifying agents*—These 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*—Adrenergic blockers are inhibited by amphetamines.

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

*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 toxic neurological 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.

*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 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:

Carcinogenicity studies of lisdexamfetamine have not been performed.

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.

Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK<sup>+</sup> mouse lymphoma assay *in vitro*.

Amphetamine (*d* to *l* enantiomer 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.

**Pregnancy:** Pregnancy Category C.

Reproduction studies of lisdexamfetamine have not been performed.

Amphetamine (*d* to *l* enantiomer 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. Fetal malformations and death have been reported in mice following parenteral administration

of dextroamphetamine doses of 50 mg/kg/day 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 amphetamine 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:** Vyvanse is indicated for use in children aged 6 to 12 years.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m<sup>2</sup> basis. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four week drug-free recovery period bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m<sup>2</sup> basis). This effect partially or fully reversed during a four week drug-free recovery period.

**Use in Children under Six Years of Age:** Lisdexamfetamine dimesylate has not been studied in 3-5 year olds. 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.

**Geriatric Use:** Vyvanse has not been studied in the geriatric population.

## ADVERSE EVENTS

The premarketing development program for Vyvanse included exposures in a total of 404 participants in clinical trials (348 pediatric patients and 56 healthy adult subjects). Of these, 348 pediatric patients (ages 6 to 12) were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study. The information included in this section is based on data from the 4-week parallel-group controlled clinical trial in pediatric patients with ADHD. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MedRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

**Adverse events associated with discontinuation of treatment:** Ten percent (21/218) of Vyvanse-treated patients discontinued due to adverse events compared to 1% (1/ 72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash (2/218 each; 1%).

**Adverse events occurring in a controlled trial:** Adverse events reported in a 4-week clinical trial in pediatric patients treated with Vyvanse or placebo are presented in the table below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following adverse events that occurred in at least 5% of the Vyvanse patients and at a rate twice that of the placebo group (Table 1): Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

Table 1 Adverse Events Reported by 2% or More of Pediatric Patients Taking Vyvanse in a 4 Week Clinical Trial

Body System	Preferred Term	Vyvanse (n=218)	Placebo (n=72)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Dry Mouth	5%	0%
	Nausea	6%	3%
	Vomiting	9%	4%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
Investigations	Weight Decreased	9%	1%
Metabolism and Nutrition	Decreased Appetite	39%	4%
Nervous System Disorders	Dizziness	5%	0%
	Headache	12%	10%
	Somnolence	2%	1%
Psychiatric Disorders	Affect lability	3%	0%
	Initial Insomnia	4%	0%
	Insomnia	19%	3%
	Irritability	10%	0%
	Tic	2%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

Note: This table only includes those events for which the incidence in patients taking Vyvanse is greater than the incidence in patients taking placebo.

The following additional adverse reactions have been associated with the use of amphetamine, amphetamine (d to l enantiomer ratio of 3:1), or Vyvanse:

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, 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.

Allergic: Urticaria, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

## DRUG ABUSE AND DEPENDENCE

## Controlled Substance Class

Vyvanse is classified as 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 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.

### *Human Studies*

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate release d-amphetamine sulfate were administered to individuals with a history of drug abuse, lisdexamfetamine 100 mg produced subjective responses on a scale of "Drug Liking Effects" "Amphetamine Effects", and "Stimulant Effects" that were significantly less than d-amphetamine immediate release 40 mg. However, oral administration of 150 mg lisdexamfetamine produced increases in positive subjective responses on these scales that were statistically indistinguishable from the positive subjective responses produced by 40 mg of oral immediate-release d-amphetamine and 200 mg of diethylpropion (C-IV).

Intravenous administration of 50 mg lisdexamfetamine to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

### *Animal Studies*

In animal studies, lisdexamfetamine produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine. In monkeys trained to self-administer cocaine, intravenous lisdexamfetamine maintained self-administration at a rate that was statistically less than that for cocaine, but greater than that of placebo.

## **OVERDOSAGE**

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

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

and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

**Treatment:** Consult with a Certified Poison Control Center for up to date guidance and advice. 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 overdose, 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 Vyvanse in the body should be considered when treating patients with overdose.

## **DOSAGE AND ADMINISTRATION**

Dosage should be individualized according to the therapeutic needs and response of the patient. Vyvanse should be administered at the lowest effective dosage.

In children with ADHD who are 6-12 years of age and are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the recommended dose. If the decision is made to increase the dose beyond 30 mg/day, daily dosage may be adjusted in increments of 20 mg/day and at approximately weekly intervals. The maximum recommended dose for children is 70 mg/day; doses greater than 70 mg/day of Vyvanse have not been studied in children. Amphetamines are not recommended for children under 3 years of age. Vyvanse has not been studied in children under 6 or over 12 years of age.

Vyvanse should be taken in the morning. Afternoon doses should be avoided because of the potential for insomnia.

Vyvanse may be taken with or without food.

Vyvanse capsules may be taken whole, or the capsule may be opened and the entire contents dissolved in a glass of water. If the patient is using the solution administration method, the solution should be consumed immediately; it should not be stored. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

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

## **HOW SUPPLIED**

Vyvanse capsules 30 mg: white body/orange cap (imprinted NRP104 30 mg), bottles of 100, NDC 59417-103-10

Vyvanse capsules 50 mg: white body/blue cap (imprinted NRP104 50 mg), bottles of 100, NDC 59417-105-10

Vyvanse capsules 70 mg: blue body/orange cap (imprinted NRP104 70 mg), bottles of 100, NDC 59417-107-10

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]

## **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.

Manufactured for: New River Pharmaceuticals Inc., Blacksburg, VA 24060. Made in USA.

Distributed by: Shire US Inc., Wayne, PA 19087

For more information call 1-800-828-2088, or visit [www.Vyvanse.com](http://www.Vyvanse.com)

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**MEDICATION GUIDE**  
**VYVANSE™**  
**(lisdexamfetamine dimesylate) CII**

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

**What is the most important information I should know about Vyvanse?**

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

**1. Heart-related problems:**

- sudden death in patients who have heart problems or heart defects
- stroke and heart attack in adults
- increased blood pressure and heart rate

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

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

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

**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 Vyvanse.**

**2. Mental (Psychiatric) problems:**

**All Patients**

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

**Children and Teenagers**

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

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

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

**What Is Vyvanse?**

Vyvanse is a central nervous system stimulant prescription medicine. **It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).** Vyvanse may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

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

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

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

**Who should not take Vyvanse?**

**Vyvanse should not be taken if you or your child:**

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

Vyvanse has not been studied in children less than 6 years old. Vyvanse is not recommended for use in children less than 3 years old.

**Vyvanse may not be right for you or your child. Before starting Vyvanse tell your or your child's doctor about all health conditions (or a family history of) including:**

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

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

**Can Vyvanse be taken with other medicines?**

**Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements.** Vyvanse and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking Vyvanse.

Your doctor will decide whether Vyvanse can be taken with other medicines.

**Especially tell your doctor if you or your child takes:**

- anti-depression medicines including MAOIs
- anti-psychotic medicines

- lithium
- blood pressure medicines
- seizure medicines
- narcotic pain medicines

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

**Do not start any new medicine while taking Vyvanse without talking to your doctor first.**

### How should Vyvanse be taken?

- **Take Vyvanse exactly as prescribed.** Vyvanse comes in 3 different strength capsules. Your doctor may adjust the dose until it is right for you or your child.
- Take Vyvanse once a day in the morning.
- Vyvanse can be taken with or without food.
- From time to time, your doctor may stop Vyvanse treatment for awhile to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking Vyvanse. Children should have their height and weight checked often while taking Vyvanse. Vyvanse treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much Vyvanse or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

### What are possible side effects of Vyvanse?

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

#### Other serious side effects include:

- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

#### Common side effects include:

- upper belly pain
- decreased appetite
- dizziness
- dry mouth
- irritability
- trouble sleeping
- nausea
- vomiting
- weight loss

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

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

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

### How should I store Vyvanse?

- Store Vyvanse in a safe place at room temperature, 59 to 86° F (15 to 30° C). Protect from light.

- **Keep Vyvanse and all medicines out of the reach of children.**

### General information about Vyvanse

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Vyvanse for a condition for which it was not prescribed. Do not give Vyvanse to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about Vyvanse. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Vyvanse that was written for healthcare professionals. For more information about Vyvanse, please contact Shire US Inc. at 1-800-828-2088 or visit [www.Vyvanse.com](http://www.Vyvanse.com).

### What are the ingredients in Vyvanse?

**Active Ingredient:** lisdexamfetamine dimesylate

**Inactive Ingredients:** microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: D&C Red #28, D&C Yellow #10, FC&C Blue #1 and FC&C red #40.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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Robert Temple  
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