

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYVANSE safely and effectively. See full prescribing information for VYVANSE.

VYVANSE® (lisdexamfetamine dimesylate) capsules, for oral use, CII  
Initial U.S. Approval: 2007

**WARNING: MISUSE, ABUSE, ADDICTION, AND DIVERSION**  
See full prescribing information for complete boxed warning.

- VYVANSE (lisdexamfetamine dimesylate) is a Schedule II controlled substance. Stimulants, such as amphetamines and methylphenidates, are subject to misuse, abuse, addiction, and criminal diversion (9)
- Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events (10)

### RECENT MAJOR CHANGES

|   |         |
|---|---------|
| Boxed Warning   | 01/2012 |
| Indications and Usage, Attention Deficit Hyperactivity Disorder (1) | 01/2012 |
| Dosage and Administration, Maintenance/Extended Treatment (2.3)     | 01/2012 |

### INDICATIONS AND USAGE

Vyvanse is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)

- Children: Efficacy was established in three short-term trials in 6-12 year olds (14)
- Adolescents: Efficacy was established in one short-term trial in 13-17 year olds (14)
- Adults: Efficacy was established in two short-term and one maintenance trials (14)

### DOSAGE AND ADMINISTRATION

- Recommended starting dose: 30 mg once daily in the morning in patients ages 6 and above (2.2)
- Increase in increments of 10 mg or 20 mg at weekly intervals if needed (2.2)
- Maximum dose: 70 mg per day (2.2)

### DOSAGE FORMS AND STRENGTHS

- Capsules: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)

### CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in Vyvanse (4)
- Use with monoamine oxidase (MAO) inhibitor: stop MAO at least 2 weeks prior to Vyvanse use (4, 7.5)

### WARNINGS AND PRECAUTIONS

- Serious Cardiovascular Reactions: Sudden death in children and adolescents with structural cardiac abnormalities or other serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults has been reported in CNS stimulant treatment at usual doses. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, or other serious heart problems (5.1)
- Increase in Blood Pressure: Monitor blood pressure and pulse in patients taking Vyvanse. Use with caution in patients for whom blood pressure increases may be problematic (5.2)
- Psychiatric Adverse Reactions: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Clinical evaluation for bipolar disorder is recommended prior to stimulant use. Monitor for aggressive behavior (5.3)
- Long-Term Suppression of Growth: Monitor height and weight in pediatric patients during treatment (5.4)
- Seizures: May lower the convulsive threshold. Discontinue if seizures develop (5.5)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$ 5% and at a rate at least twice placebo) in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

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

### DRUG INTERACTIONS

- Urinary acidifying agents may reduce blood levels of amphetamine (7.1)
- Urinary alkalinizing agents may increase blood levels of amphetamine (7.2)
- The effects of adrenergic blockers, antihistamines, and antihypertensives, may be reduced by amphetamines (7.4)
- The effects of tricyclic antidepressants, meperidine, phenobarbital, and phenytoin, and norepinephrine may be potentiated by amphetamines (7.5)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to the mother (8.3)
- Pediatric Use: Safety and Effectiveness not established in pediatric patients below 6 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2012

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## FULL PRESCRIBING INFORMATION

### WARNING: POTENTIAL FOR MISUSE, ABUSE, ADDICTION, AND DIVERSION

**VYVANSE (lisdexamfetamine dimesylate) is a Schedule II controlled substance. Stimulants, such as amphetamines and methylphenidates, are subject to misuse, abuse, addiction, and criminal diversion [see Drug Abuse and Dependence (9)].**

**Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events [see Overdosage (10)].**

## 1 INDICATIONS AND USAGE

### Attention Deficit Hyperactivity Disorder

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 three short-term controlled trials in children ages 6 to 12 years, one short-term controlled trial in adolescents ages 13 to 17 years, and two short-term controlled trials in adults who met DSM-IV-TR® criteria for ADHD, and one maintenance trial in adults [see Clinical Studies (14)].

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV®) implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 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 6 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 6 of the following symptoms (or adult equivalent 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 also 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

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 patients with this syndrome. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational/vocational 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 patient's symptoms and on the level of functional impairment.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Instructions for Use

Vyvanse should be taken in the morning with or without food. Afternoon doses should be avoided because of the potential for insomnia.

Vyvanse capsules may be taken whole, or the capsule may be opened and the entire contents dissolved in a glass of **water**. The solution should be consumed **immediately** and 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.

### 2.2 Initiation treatment

The recommended starting dose is 30 mg once daily in the morning in patients ages 6 and above. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum dose of 70 mg/day; Doses greater than 70 mg/day have not been studied.

Dosage should be individualized according to the therapeutic needs and response of the patient. Vyvanse should be administered at the lowest effective dosage. The least amount of Vyvanse feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

### 2.3 Maintenance/Extended Treatment

It is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The benefit of maintaining adult patients (ages 18-55 years) with ADHD on Vyvanse was demonstrated in a controlled randomized withdrawal trial [see Clinical Studies (14)]. Subjects assigned to Vyvanse in the randomized withdrawal phase continued on the same dose used to confirm response in the open-label phase.

The physician who elects to use Vyvanse for extended periods should periodically re-evaluate the long-term usefulness of Vyvanse for the individual patient. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment.

## 3 DOSAGE FORMS AND STRENGTHS

Vyvanse capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg)  
Vyvanse capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg)  
Vyvanse capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg)  
Vyvanse capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg)  
Vyvanse capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg)  
Vyvanse capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg)

## 4 CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports [see Adverse Reactions (6.2)].
- Concurrent administration of monoamine oxidase (MAO) inhibitors because MAOIs potentially can result in hypertensive crisis. Vyvanse should not be given for at least 14 days after discontinuation of an MAO inhibitor [see Drug Interactions (7.3)]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Cardiovascular Reactions

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.

#### Adults

Sudden death, 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 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.

#### Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications

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

### 5.2 Increased Blood Pressure

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mm Hg) 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.

### 5.3 Psychiatric Adverse Reactions

#### Pre-existing Psychosis

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

#### 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.

#### 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 a 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 of ADHD should be monitored for the appearance of, or worsening of, aggressive behavior or hostility.

#### 5.4 Long-Term Suppression of Growth

In pediatric patients, growth (weight and height) should be monitored during treatment with stimulants, including Vyvanse, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Adverse Reactions* (6.1)].

#### 5.5 Seizures

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, Vyvanse should be discontinued.

#### 5.6 Visual Disturbance

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

#### 5.7 Tics

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome should precede use of Vyvanse.

### 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling

- Serious Cardiovascular Reactions [see *Warnings and Precautions* (5.1)]
- Increased Blood Pressure [see *Warnings and Precautions* (5.2)]
- Psychiatric Adverse Reactions [see *Warnings and Precautions* (5.3)]
- Long-Term Suppression of Growth in Pediatric Patients [see *Warnings and Precautions* (5.4)]
- Seizures [see *Warnings and Precautions* (5.5)]
- Visual Disturbance [see *Warnings and Precautions* (5.6)]
- Tics [see *Warnings and Precautions* (5.7)]

#### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The premarketing development program for Vyvanse included exposures in a total of 995 participants in clinical trials (348 pediatric patients aged 6 to 12 years, 233 adolescent patients aged 13 to 17 years, 358 adult patients and 56 healthy adult subjects). Of these, 348 pediatric (aged 6 to 12) patients 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, 233 adolescent (aged 13 to 17) patients were evaluated in one controlled clinical study, and 358 adult patients were evaluated in one controlled clinical study and one open-label extension study. The information included in this section is based on data from the 4-week parallel-group controlled clinical studies in pediatric and adult patients with ADHD [see *Clinical Studies* (14)]. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse reactions during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reactions categories. The stated frequencies of adverse reactions represent the proportion of individuals who experienced an adverse reaction of the type listed at least once.

#### Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled pediatric (ages 6 to 12 years) trial, 9% (20/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) who received placebo. The most frequent adverse reactions 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%).

In the controlled adolescent (ages 13 to 17 years) trial, 4% (10/233) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/77) who received placebo. The most frequent adverse reactions leading to discontinuation and considered to be drug-related were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of Vyvanse-treated patients discontinued due to adverse reactions compared to 2% (1/62) who received placebo. The most frequent adverse reactions 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 insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

#### Adverse Reactions Occurring at an Incidence of 2% or More Among Vyvanse Treated Patients in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with Vyvanse or placebo are presented in Tables 1, 2, and 3 below.

#### Pediatric

**Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) 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%             |
|   | Vomiting              | 9%              | 4%             |
|   | Nausea                | 6%              | 3%             |
|   | Dry Mouth             | 5%              | 0%             |
| 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%             |
|   | Somnolence            | 2%              | 1%             |
| Psychiatric Disorders                               | Insomnia <sup>a</sup> | 23%             | 3%             |
|   | Irritability          | 10%             | 0%             |
|   | Affect lability       | 3%              | 0%             |
|   | Tic                   | 2%              | 0%             |
| Skin and Subcutaneous Tissue Disorders              | Rash                  | 3%              | 0%             |

<sup>a</sup> Insomnia includes the following preferred terms reported in the study: Initial Insomnia, Insomnia.

Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

**Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients Taking Vyvanse in a 4-Week Clinical Trial**

| Body System                | Preferred Term        | Vyvanse (n=233) | Placebo (n=77) |
|----------------------------|-----------------------|-----------------|----------------|
| Gastrointestinal Disorders | Dry Mouth             | 4%              | 1%             |
| Investigations             | Weight Decreased      | 9%              | 0%             |
| Metabolism and Nutrition   | Decreased Appetite    | 34%             | 3%             |
| Psychiatric Disorders      | Insomnia <sup>b</sup> | 13%             | 4%             |

<sup>b</sup> Insomnia includes the following preferred terms reported in the study: Initial Insomnia, Insomnia.

Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

#### Adult

**Table 3 Adverse Reactions Reported by 2% or More of Adult Patients Taking Vyvanse in a 4-Week Clinical Trial**

| Body System   | Preferred Term           | Vyvanse (n=358) | Placebo (n=62) |
|---|--------------------------|-----------------|----------------|
| Gastrointestinal Disorders                          | Dry Mouth                | 26%             | 3%             |
|   | Diarrhea                 | 7%              | 0%             |
|   | Nausea                   | 7%              | 0%             |
| General Disorder and Administration Site Conditions | Feeling Jittery          | 4%              | 0%             |
| Investigations                                      | Blood Pressure Increased | 3%              | 0%             |
|   | Heart Rate Increased     | 2%              | 0%             |
| Metabolism and Nutrition Disorders                  | Decreased Appetite       | 27%             | 3%             |
|   | Anorexia                 | 5%              | 0%             |
| Nervous System Disorders                            | Tremor                   | 2%              | 0%             |
| Psychiatric Disorders                               | Insomnia <sup>c</sup>    | 27%             | 8%             |
|   | Anxiety                  | 6%              | 0%             |
|   | Agitation                | 3%              | 0%             |
|   | Restlessness             | 3%              | 0%             |
| Respiratory, Thoracic, and Mediastinal Disorders    | Dyspnea                  | 2%              | 0%             |
| Skin and Subcutaneous Tissue Disorders              | Hyperhidrosis            | 3%              | 0%             |

<sup>c</sup> Insomnia includes the following preferred terms reported in the study: Initial Insomnia, Insomnia, Middle Insomnia.

Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

In addition, adverse reactions observed at a rate of less than 2% in adults included decreased libido and erectile dysfunction.

#### Weight Loss and Slowing Growth Rate in Pediatric Patients

In a controlled trial of Vyvanse 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 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of Vyvanse, compared to a 1 pound 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 Vyvanse 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 percentiles at baseline and 12 months were 60.6 and 47.2, respectively). In a 4-week controlled trial of Vyvanse in adolescents ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of Vyvanse, compared to a 2.0 pound weight gain for patients receiving placebo.

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 pounds and -2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

#### Weight Loss in Adults

In the controlled adult trial, mean weight loss after 4 weeks of therapy was 2.8 pounds, 3.1 pounds, and 4.3 pounds, for patients receiving final doses of 30 mg, 50 mg, and 70 mg of Vyvanse, respectively, compared to a mean weight gain of 0.5 pounds for patients receiving placebo.

### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiac Disorders** – Palpitations, cardiomyopathy

**Eye Disorders** – Mydriasis, diplopia

**Hepatobiliary Disorders** – Eosinophilic hepatitis

**Immune System Disorders** – Anaphylactic reaction, hypersensitivity

**Nervous System Disorders** – Dyskinesia

**Psychiatric Disorder** – Depression, dysphoria, euphoria, logorrhoea, dermatillomania

**Skin and Subcutaneous Tissue Disorder** – Stevens-Johnson Syndrome, angioedema, urticaria

## **7 DRUG INTERACTIONS**

### **7.1 Agents that Lower Blood Levels of Amphetamines**

#### 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.

#### Methamphetamine Therapy

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

### **7.2 Agents that Increase Blood Levels of Amphetamines**

#### Urinary Alkalinizing Agents

These agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion.

### **7.3 Monoamine Oxidase Inhibitors**

Dextroamphetamine is known to inhibit monoamine oxidase.

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. Do not administer Vyvanse during or within 14 days following the administration of monoamine oxidase inhibitors [see *Contraindications (4)*].

### **7.4 Agents Whose Effects May be Reduced by Amphetamines**

#### Adrenergic Blockers

Adrenergic blockers are inhibited by amphetamines.

#### Antihistamines

Amphetamines may counteract the sedative effect of antihistamines.

#### Antihypertensives

Amphetamines may antagonize the hypotensive effects of antihypertensives.

#### Veratrum Alkaloids

Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

#### Ethosuximide

Amphetamines may delay intestinal absorption of ethosuximide.

### **7.5 Agents Whose Effects May be Potentiated by Amphetamines**

#### Antidepressants, Tricyclic

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

#### Meperidine

Amphetamines potentiate the analgesic effect of meperidine.

#### Norepinephrine

Amphetamines 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.

### **7.6 Agents that May Reduce the Effects of Amphetamines**

#### Chlorpromazine

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

#### Haloperidol

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

#### Lithium Carbonate

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

### **7.7 Agents that May Potentiate the Effects of Amphetamines**

#### Propoxyphene Overdosage

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

### **7.8 Drug/Laboratory Test Interactions**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

There are no adequate and well-controlled studies with Vyvanse in pregnant women. Vyvanse is an amphetamine and its sympathomimetic effects on placental perfusion and fetal blood flow are unknown. Adverse pregnancy outcomes, including premature delivery and low birth weight have been seen in infants born to mothers dependent on amphetamines. Animal reproduction studies performed with lisdexamfetamine dimesylate showed no effects on embryofetal morphological development and survival. Long-term neurochemical and behavioral effects have been seen in animal developmental studies using clinically relevant doses of amphetamine (d- or d,l-). Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Human Data

Available data in women using amphetamines during pregnancy do not show a clear increased risk of major congenital malformations. Two case control studies of over a thousand patients exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities.

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight and may experience feeding difficulties and symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

#### Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 4 and 27 times, respectively, the maximum recommended human dose of 70 mg/day given to adolescents, on a mg/m<sup>2</sup> body surface area basis.

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 longterm neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

### 8.3 Nursing Mothers

Amphetamines are excreted into human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years [see *Adverse reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*]. The long-term efficacy of amphetamines, including Vyvanse, in pediatric patients have not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

#### Long Term Growth Suppression

Growth should be monitored during treatment with stimulants, including Vyvanse, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.4)*, *Adverse Reactions (6.1)*].

#### Juvenile Animal Data

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate 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 for a child. 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 dimesylate 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 for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

### 8.5 Geriatric Use

Clinical studies of Vyvanse did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Vyvanse is classified as a Schedule II controlled substance.

### 9.2 Abuse

Amphetamines have been extensively abused. 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 dimesylate 100 mg produced subjective responses on a scale of "Drug Liking Effects" (primary endpoint) that were significantly less than d-amphetamine immediate-release 40 mg. However, oral administration of 150 mg lisdexamfetamine dimesylate produced increases in positive subjective responses on this scale 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 dimesylate 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 dimesylate produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine. In monkeys trained to self-administer cocaine, intravenous lisdexamfetamine dimesylate maintained self-administration at a rate that was statistically less than that for cocaine, but greater than that of placebo.

### 9.3 Dependence

Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high-dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

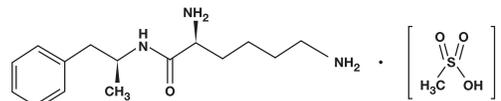
## 10 OVERDOSAGE

Consult with a Certified Poison Control Center for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

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.

## 11 DESCRIPTION

Vyvanse (lisdexamfetamine dimesylate), a CNS stimulant, is 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<sub>15</sub>H<sub>25</sub>N<sub>3</sub>O•(CH<sub>3</sub>O<sub>2</sub>S)<sub>2</sub>, 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 20 mg, 30 mg, 40 mg, 50 mg, 60 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: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted primarily in blood due to the hydrolytic activity of red blood cells 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 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*.

### 12.3 Pharmacokinetics

Pharmacokinetic studies of dextroamphetamine after oral administration of lisdexamfetamine have been conducted in pediatric patients ages 6 to 12 years with ADHD and in healthy adult volunteers.

In 18 pediatric patients (ages 6 to 12 years) 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 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 ages 6 to 12 years.

There is no unexpected accumulation of dextroamphetamine AUC at steady state in healthy adults and no accumulation of lisdexamfetamine 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 AUCs 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 dimesylate for 7 days. Weight/Dose normalized AUC and C<sub>max</sub> values were the same in pediatric patients ages 6 to 12 years following single doses of 30-70 mg.

#### Metabolism and Excretion

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). 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% to intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine 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.

## Drug Interactions Studies

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.

Extended release guanfacine: In a drug interaction study (N=40), administration of an extended release guanfacine (4 mg) in combination with Vyvanse (50mg) increased guanfacine maximum plasma concentration by 19%, whereas, exposure (area under the curve; AUC) was increased by 7%. These small changes are not expected to be clinically meaningful. In this study, no effect on d-amphetamine exposure was observed following co-administration of extended release guanfacine and Vyvanse.

## Special Populations

### Age

The pharmacokinetics of dextroamphetamine is similar in children (ages 6 to 12 years) and adolescent (ages 13 to 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis/ Mutagenesis and Impairment of Fertility

Carcinogenicity studies of lisdexamfetamine dimesylate 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.

### 13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

## 14 CLINICAL STUDIES

The short-term efficacy of Vyvanse in the treatment of ADHD was established on the basis of three controlled trials in children ages 6 to 12 years (Study 1, 2, and 3), one controlled trial in adolescents ages 13 to 17 years (Study 4), and two controlled trials in adults (Study 5 and 6) who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for ADHD. Maintenance of efficacy after long-term use of at least 6 months was demonstrated in one randomized withdrawal trial in adults (Study 7) [see *Indications and Usage (1)*].

**Table 4: Summary of Primary Efficacy Results from Short-term Studies**

| Study No.<br>(Age range) | Primary Endpoint    | Measure  | Placebo | Vyvanse<br>30 mg/day       | Vyvanse<br>50 mg/day       | Vyvanse<br>70 mg/day       | Vyvanse<br>30, 50, or 70<br>mg/day |
|--------------------------|---------------------|--|---------|----------------------------|----------------------------|----------------------------|------------------------------------|
| 1<br>(6 -12 years)       | ADHD-RS-IV          | Mean Baseline Score                                      | 42.4    | 43.2                       | 43.3                       | 45.1                       | -                                  |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -15.58<br>(-20.78, -10.38) | -17.21<br>(-22.33, -12.08) | -20.49<br>(-25.63, -15.36) | -                                  |
| 2<br>(6 -12 years)       | Average<br>SKAMP-DS | Mean Pre-dose Score <sup>b</sup>                         | -       | -                          | -                          | -                          | -                                  |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -                          | -                          | -                          | -0.9<br>(-1.1, -0.7)               |
| 3<br>(6 -12 years)       | Average<br>SKAMP-DS | Mean Pre-dose Score                                      | 0.71    | -                          | -                          | -                          | 0.88                               |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -                          | -                          | -                          | -0.74<br>(-0.85, -0.63)            |
| 4<br>(13 -17 years)      | ADHD-RS-IV          | Mean Baseline Score                                      | 38.5    | 38.3                       | 37.3                       | 37.0                       | -                                  |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -5.5<br>(-9.7, -1.3)       | -8.3<br>(-12.5, -4.1)      | -7.9<br>(-12.1, -3.8)      | -                                  |
| 5<br>(18 -55 years)      | ADHD-RS-IV          | Mean Baseline Score                                      | 39.4    | 40.5                       | 40.8                       | 41.0                       | -                                  |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -8.04<br>(-12.14, -3.95)   | -9.16<br>(-13.25, -5.08)   | -10.41<br>(-14.49, -6.33)  | -                                  |
| 6<br>(18 -55 years)      | Average<br>PERMP    | Mean Pre-dose Score                                      | 261.4   | -                          | -                          | -                          | 260.1                              |
|                          |                     | LS Mean difference<br>from Placebo (95% CI) <sup>a</sup> | -       | -                          | -                          | -                          | 23.4<br>(15.6, 31.2)               |

<sup>a</sup> Difference (drug – placebo) in Least Squares (LS) Mean for the primary efficacy outcome along with 95% confidence intervals. If there are multiple Vyvanse dose arms, adjusted CIs are reported. For ADHD-RS-IV and SKAMP-DS scales, a higher score indicates more severe symptoms, so a negative LS mean difference indicates improvement from placebo (studies 1-5). For the PERMP scale, a higher score indicates less severe symptoms, so a positive LS mean difference indicates improvement from placebo.

<sup>b</sup> Pre-dose SKAMP-DS was not collected

CI: Confidence interval

## Pediatric

A double-blind, randomized, placebo-controlled, parallel-group study (Study 1) was conducted in children ages 6 to 12 years (N=290) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of Vyvanse or placebo once daily in the morning for a total of four weeks of treatment. All patients receiving Vyvanse were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), a measure of the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All Vyvanse dose groups were superior to placebo in the primary efficacy outcome. Mean effects at all doses were fairly similar, although the highest dose (70 mg/day) was numerically superior to both lower doses (Study 1 in Table 4). The effects were maintained throughout the day based on parent ratings (Conners' 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 (Study 2) was conducted in children ages 6 to 12 years (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<sup>®</sup>, patients were randomly assigned to continue the same dose of Adderall XR (10 mg, 20 mg, or 30 mg), Vyvanse (30 mg, 50 mg, or 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 7 assessments conducted at 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose were observed between patients who received Vyvanse compared to patients who received placebo (Study 2 in Table 4). The drug effect was similar for all 7 sessions.

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 3) was conducted in children ages 6 to 12 years (N=129) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose titration with Vyvanse (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue Vyvanse 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 SKAMP-Department scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients who received Vyvanse compared to patients who received placebo (Study 3 in Table 4, Figure 1).

A double-blind, randomized, placebo-controlled, parallel-group study (Study 4) was conducted in adolescents ages 13 to 17 years (N=314) who met DSM-IV criteria for ADHD. In this study, patients were randomized in a 1:1:1 ratio to a daily morning dose of Vyvanse (30 mg/day, 50 mg/day or 70 mg/day) or placebo for a total of four weeks of treatment. All patients receiving Vyvanse were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were

titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), a measure of the core symptoms of ADHD. Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All Vyvanse dose groups were superior to placebo in the primary efficacy outcome (Study 4 in Table 4).

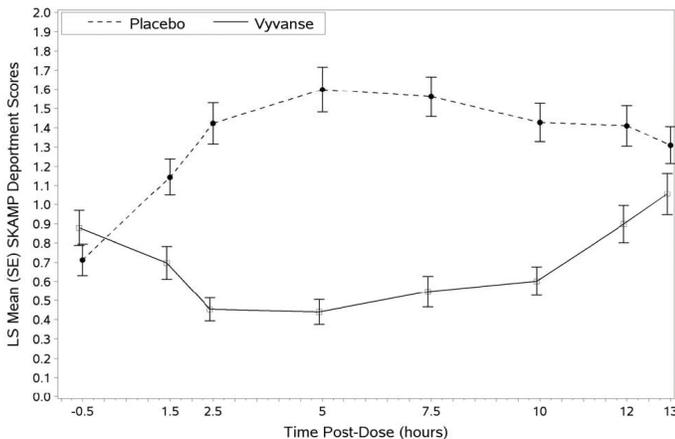
#### Adult

A double-blind, randomized, placebo-controlled, parallel-group study (Study 5) was conducted in adults ages 18 to 55 (N=420) who met DSM-IV criteria for ADHD. In this study, patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of Vyvanse or placebo for a total of four weeks of treatment. All patients receiving Vyvanse were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), a measure of the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All Vyvanse dose groups were superior to placebo in the primary efficacy outcome (Study 5 in Table 4).

The second study was a multi-center, randomized, double-blind, placebo-controlled, crossover design, modified analog classroom study (Study 6) of Vyvanse to simulate a workplace environment in 142 adults ages 18 to 55 who met DSM-IV-TR criteria for ADHD. There was a 4-week open-label, dose optimization phase with Vyvanse (30 mg/day, 50 mg/day, or 70 mg/day in the morning). Patients were then randomized to one of two treatment sequences: 1) Vyvanse (optimized dose) followed by placebo, each for one week, or 2) placebo followed by Vyvanse, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP). The PERMP is a skill-adjusted math test that measures attention in ADHD. Vyvanse treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose (Study 6 in Table 4, Figure 2).

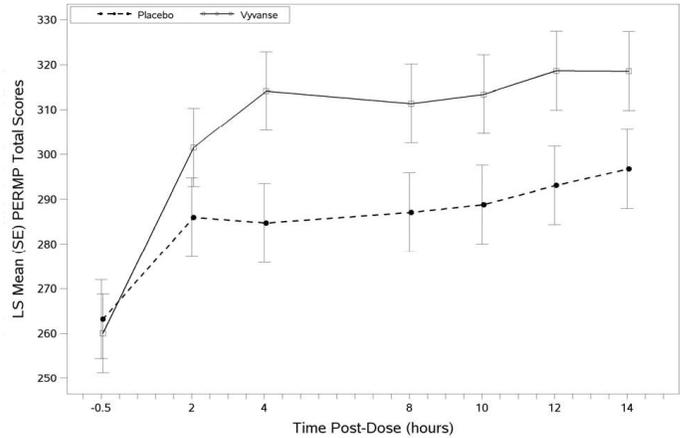
Maintenance of Efficacy Study (Study 7) - A double-blind, placebo-controlled, randomized withdrawal design study was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV with adult prompts criteria for ADHD. At study entry, patients must have had documentation of treatment with Vyvanse for a minimum of 6 months and had to demonstrate treatment response as defined by CGI-S  $\leq 3$  and Total Score on the ADHD-RS with adult prompts  $< 22$ . ADHD-RS Total Score is a measure of core symptoms of ADHD. Patients that maintained treatment response at week 3 of open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of Vyvanse (N=56) or switched to placebo (N=60) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. Maintenance of efficacy for patients treated with Vyvanse was demonstrated by the significantly lower proportion of treatment failure (8.9%) compared to patients receiving placebo (75%) at endpoint during the double-blind randomized withdrawal phase (Figure 3). The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS with adult prompts total score and CGI-S were observed. Treatment failure was defined as a  $\geq 50\%$  increase (worsening) in the ADHD-RS with adult prompts Total Score and  $\geq 2$ -point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase (Study 7, Figure 3).

**Figure 1 LS Mean SKAMP Department Subscale Score at Visit 5/6 by Treatment and Time-point for Children Ages 6 to 12 (Study 3)**



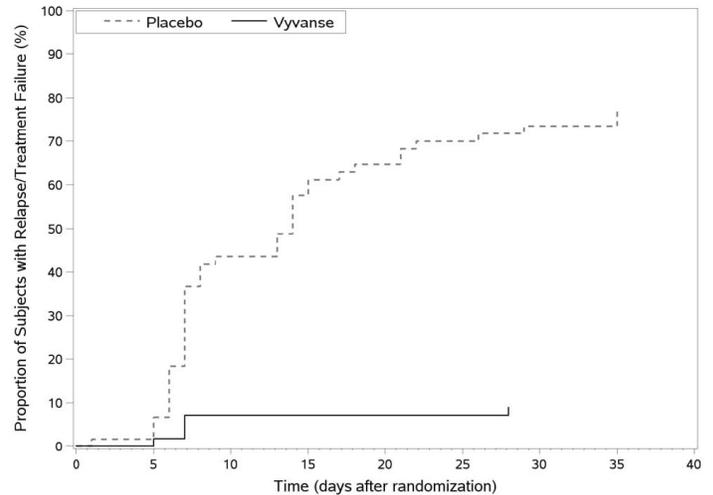
Higher score on the SKAMP-Department scale indicates more severe symptoms

**Figure 2 LS Mean (SE) PERMP Total Score at Visit 5/6 by Treatment and Time-point for Adults Ages 18 to 55 (Study 6)**



Higher score on the PERMP scale indicates less severe symptoms.

**Figure 3 Kaplan-Meier Estimation of Proportion of Patients with Treatment Failure (Study 7)**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Vyvanse capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10

Vyvanse capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10

Vyvanse capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10

Vyvanse capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10

Vyvanse capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10

Vyvanse capsules 70 mg: blue body/orange cap (imprinted with S489 and 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]

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

### 17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Vyvanse 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 attached to the package insert.

**17.2 Controlled Substance Status/Potential for Abuse, Misuse, and Dependence**

Patients should be advised that Vyvanse is a federally controlled substance because it can be abused or lead to dependence. Additionally, it should be emphasized that Vyvanse should be stored in a safe place to prevent misuse and/or abuse. Patient history (including family history) of abuse or dependence on alcohol, prescription medicines, or illicit drugs should be evaluated [see *Drug Abuse and Dependence (9.2, 9.3)*].

**17.3 Serious Cardiovascular Risks**

There is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with Vyvanse use. Contact the doctors immediately if patients develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [see *Warnings and Precautions (5.1)*].

**17.4 Psychiatric Risks**

Prior to initiating treatment with Vyvanse, 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/or depression. Additionally, Vyvanse therapy at usual doses may cause treatment-emergent psychotic or manic symptoms in patients without prior history of psychotic symptoms or mania [see *Warnings and Precautions (5.3)*].

**17.5 Long-Term Suppression of Growth**

Growth should be monitored during treatment with Vyvanse, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.4)*].

**17.6 Pregnancy**

Patients should tell their physicians if they become pregnant or intend to become pregnant during Vyvanse treatment. Patients should be advised of the potential fetal effects from the use of Vyvanse and other amphetamines during pregnancy [see *Use in Specific Populations (8.1)*].

**17.7 Nursing**

Patients should be advised to notify their physician if they are breastfeeding or intend to breastfeed an infant [see *Use in Specific Populations (8.3)*].

**17.8 Impairment in Ability to Operate Machinery or Vehicles**

Vyvanse may impair patient's ability of engaging in potentially dangerous activities such as operating machinery or vehicles. Patients should find out how Vyvanse will affect them before engaging in potentially dangerous activities.

**Pharmacist: Medication Guide to be dispensed to patients.**

Manufactured for: Shire US Inc., Wayne, PA 19087

Made in USA

For more information call 1-800-828-2088

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VYV-03398



**MEDICATION GUIDE**  
**VYVANSE® [VĪ - vāns]**  
**(lisdexamfetamine dimesylate) CII**  
**Capsules**

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 your or your child's treatment with Vyvanse.

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

**Vyvanse is a stimulant medicine. Some people have had the following problems when taking stimulant medicines such as Vyvanse:**

**1. Heart-related problems including:**

- **sudden death in people 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 should check you or your child carefully for heart problems before starting Vyvanse.

Your doctor should check your 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 including:**

**In Children, Teenagers, and Adults:**

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

**In Children and Teenagers**

- **new psychotic symptoms such as:**
  - **hearing voices**
  - **believing things that are not true**
  - **being suspicious**
- **new manic symptoms**

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

**Call your doctor right away if you or your child has 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**
- **being suspicious**

**What Is Vyvanse?**

Vyvanse is a central nervous system stimulant prescription medicine. Vyvanse 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 has ever abused or been dependent on alcohol, prescription medicines or street drugs.

It is not known if Vyvanse is safe and effective in children under 6 years of age.

**Who should not take Vyvanse?**

**Do not take Vyvanse if you or your child:**

- is taking or has 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.

**What should I tell my doctor before taking Vyvanse?**

**Before you or your child takes Vyvanse, tell your doctor if you or your child has or if there is a family history of:**

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

**Tell your doctor if:**

- you or your child is pregnant or plan to become pregnant. It is not known if Vyvanse will harm your unborn baby.
- you or your child is breastfeeding or plan to breastfeed. Vyvanse passes into breast milk. Discuss with your doctor before you breastfeed while you are taking Vyvanse.

**Tell your doctor about all of the medicines that you or your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.**

Vyvanse can affect the way other medicines work, and other medicines may affect how Vyvanse works. Using Vyvanse with other medicines can cause serious side effects.

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

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines that you or your child takes. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

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

**How should I take Vyvanse?**

- Take Vyvanse exactly as your doctor tells you to take it.
- Your doctor may change your 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.
- Vyvanse capsules may be taken whole or opened and the powder may be mixed in a glass of water. Use all of the powder from the capsule so you get all of the medicine. Drink the entire glass of water right away after mixing.

- Your doctor may sometimes stop Vyvanse treatment for a while to check your ADHD symptoms.
- Your doctor may do regular checks of your 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, call your doctor or poison control center right away, or get to the nearest hospital emergency room.

### **What should I avoid while taking Vyvanse?**

Do not drive, operate machinery, or do other dangerous activities until you know how Vyvanse affects you.

### **What are possible side effects of Vyvanse?**

#### **Vyvanse may cause serious side effects, including:**

- See **“What is the most important information I should know about Vyvanse?”**.
- slowing of growth (height and weight) in children
- seizures, mainly in people with a history of seizures
- eyesight changes or blurred vision
- worsening of sudden, repeated movements or sounds (tics) and Tourette’s syndrome in people who already have these problems

The most common side effects of Vyvanse include:

- anxiety
- decreased appetite
- diarrhea
- dizziness
- dry mouth
- irritability
- loss of appetite
- nausea
- trouble sleeping
- upper stomach pain
- vomiting
- weight loss

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

These are not all the possible side effects of Vyvanse. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store Vyvanse?**

- Store Vyvanse at room temperature between 59°F to 86°F.
- Protect Vyvanse from light.

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

### **General information about the safe and effective use of 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.

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 is written for healthcare professionals.

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

### **What are the ingredients in Vyvanse?**

**Active Ingredient:** lisdexamfetamine dimesylate

**Inactive Ingredients:** microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells (imprinted

with NRP104) contain gelatin, titanium dioxide, and 1 or more of the following: D&C Red #28, D&C Yellow #10, FD&C Blue #1, FD&C Green #3, and FD&C Red #40. The capsule shells (imprinted with S489) contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide.

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

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