

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: ABUSE AND DEPENDENCE
See full prescribing information for complete boxed warning.

- CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. (5.1, 9.2, 9.3)
- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. (5.1, 9.2)

RECENT MAJOR CHANGES

Boxed Warning	XX/2012
Indications and Usage	XX/2012
Dosage and Administration	XX/2012
Warnings and Precautions	XX/2012

INDICATIONS AND USAGE

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

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 or 20 mg at weekly intervals if needed (2.2)
- Maximum dose: 70 mg per day (2.2)
- Prior to treatment, assess for presence of cardiac disease (2.3)

DOSAGE FORM 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, or within 14 days of the last MAO inhibitor dose (4, 7.2)

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions:* Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. (5.4)
- *Suppression of Growth:* Monitor height and weight in pediatric patients during treatment (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

DRUG INTERACTIONS

- Agents and conditions that alter urinary pH can impact the urinary excretion and half-life of amphetamine. Acidifying agents decrease the half-life of amphetamine, while alkalinizing agents increase the half-life of amphetamine. Adjust the dose accordingly. (7.1)

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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2012

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy [see *Warnings and Precautions (5.1)*, and *Drug Abuse and Dependence (9.2, 9.3)*].

1 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 three short-term controlled trials in children ages 6 to 12 years, one short-term controlled trial in adolescents ages 13 to 17 years, two short-term controlled trials in adults, and one maintenance trial in adults [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions for Use

Take Vyvanse in the morning with or without food; avoid afternoon doses because of the potential for insomnia. Vyvanse may be administered in one of the following ways:

- Take Vyvanse capsules whole, or
- Open capsules and empty and mix the entire contents in a glass of **water**. If the contents include any compacted powder, a spoon may be used to break apart the powder in the water. The content should be stirred until completely dispersed. Consume the full glass of water **immediately**. It should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass once the water is consumed. Do not take anything less than one capsule per day, and a single capsule should not be divided.

2.2 Dosing Information

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. Patients may be maintained on their optimal dose [see *Clinical Studies (14)*].

2.3 Important Information Prior to Dosing

Prior to treating children, adolescents, and adults with CNS stimulants, assess for the presence of cardiac disease (e.g., a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) [see *Warnings and Precautions (5.2)*].

To reduce the abuse of CNS stimulants including Vyvanse, assess the risk of abuse, prior to prescribing. After prescribing, keep careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and re-evaluate the need for Vyvanse use [see *Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9.2, 9.3)*].

3 DOSAGE FORM AND STRENGTHS

Capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg)

Capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg)

Capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg)

Capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg)

Capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg)

Capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg)

4 CONTRAINDICATIONS

Vyvanse is contraindicated in patients with:

- 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 inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur [*see Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Drug Abuse and Dependence (9.2, 9.3)*].

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing the CNS stimulant. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

5.5 Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Vyvanse. In a 4-week, placebo-controlled trial of Vyvanse in patients ages 6 to 12 years old, there was a dose-related decrease in weight in the Vyvanse groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height [*see Adverse Reactions (6.1)*].

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 (5.2)*]
- Blood Pressure and Heart Rate Increases [*see Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [*see Warnings and Precautions (5.4)*]
- Suppression of Growth in Pediatric Patients [*see Warnings and Precautions (5.5)*]

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 safety data in this section is based on data from the 4-week parallel-group controlled clinical studies of Vyvanse in pediatric and adult patients with ADHD [*see Clinical Studies (14)*].

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled trial in patients ages 6 to 12 years (Study 1), 9% (20/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (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 instances for each adverse reaction, i.e., 2/218 (1%)].

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

In the controlled adult trial (Study 5), 6% (21/358) of Vyvanse-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (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%).

The most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) reported 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.

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 (Study 1), adolescent patients ages 13 to 17 years (Study 4), and adult patients (Study 5) treated with Vyvanse or placebo are presented in Tables 1, 2, and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

	Vyvanse (n=218)	Placebo (n=72)
Decreased Appetite	39%	4%
Insomnia	23%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

	Vyvanse (n=233)	Placebo (n=77)
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients Taking Vyvanse and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 5)

	Vyvanse	Placebo
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	(n=358)	(n=62)
Decreased Appetite	27%	2%
Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Blood Pressure Increased	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Weight Decreased	3%	0%
Dyspnea	2%	0%
Heart Rate Increased	2%	0%
Tremor	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on Vyvanse and 0% on placebo; decreased libido was observed in 1.4% of subjects on Vyvanse and 0% on placebo.

Weight Loss and Slowing Growth Rate in Pediatric Patients

In a controlled trial of Vyvanse in children ages 6 to 12 years (Study 1), 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. [See *Warnings and Precautions*, 5.5]

Weight Loss in Adults

In the controlled adult trial (Study 5), 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. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, and seizures.

7 DRUG INTERACTIONS

7.1 Agents and Conditions that Alter Urinary pH and Impact the Urinary Excretion and Half-life of Amphetamine

Ascorbic acid and other agents and conditions that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents and conditions that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine. Adjust the dose accordingly.

7.2 Monoamine Oxidase Inhibitors

Do not administer Vyvanse concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [*see Contraindications (4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Clinical Considerations

Amphetamines, such as Vyvanse, cause vasoconstriction and thereby may decrease placental perfusion. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

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 in total exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities.

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/m² 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 long-term 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. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. 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.

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 (5.5), Adverse Reactions (6.1)*].

Juvenile Animal Data

Studies conducted in juvenile rats and dogs at clinically relevant doses showed growth suppression that partially or fully reversed in dogs and female rats but not in male rats after a four-week drug-free recovery period.

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/m² 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/m² 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 start 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 contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including Vyvanse, other amphetamines, and methylphenidate-containing products have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [*see Overdosage (10)*].

To reduce the abuse of CNS stimulants, including Vyvanse, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for Vyvanse use.

Studies of Vyvanse in Drug Abusers

A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of Vyvanse, 40 mg of immediate-release d-amphetamine sulphate (a controlled II substance), and 200 mg of diethylpropion hydrochloride (a controlled IV substance). Vyvanse 100 mg produced significantly less "Drug Liking Effects" as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of Vyvanse demonstrated similar "Drug-Liking Effects" compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

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.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) may occur during the chronic therapy of CNS stimulants including Vyvanse.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including Vyvanse. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

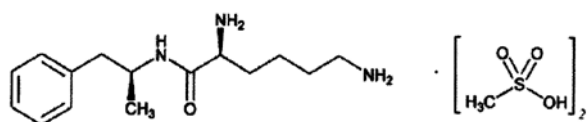
10 OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, 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 $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$, 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 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. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. 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 patients ages 6 to 12 years with ADHD and in healthy adult volunteers.

In 18 patients ages 6 to 12 years with ADHD, the T_{max} 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_{max} 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 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_{max} of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of Vyvanse capsules but prolongs T_{max} 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_{max} 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_{max} 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.

A steady-state drug interaction study with venlafaxine 225 mg and 70 mg of lisdexamfetamine resulted in a 5% decrease in d-amphetamine AUC_{0-tau} and maximum plasma concentration values. Venlafaxine AUC_{0-tau} and C_{max} increased 13% and 10% in the study.

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.

Dextroamphetamine clearance decreases in adults ages 65-75 (26% in women and 10% in men).

Gender

Systemic exposure to dextroamphetamine is similar for men and women given the same mg/kg dose. In adults ages 55-64, d-amphetamine C_{max} and AUC were 15% and 13% higher, respectively, in females compared to males.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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.

Mutagenesis

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⁺ mouse lymphoma assay *in vitro*.

Impairment of Fertility

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 (Studies 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 – text revision (DSM-IV-TR) criteria for ADHD. Maintenance of efficacy after

long-term use (at least 6 months) of Vyvanse in the treatment of ADHD was demonstrated in one randomized withdrawal trial in adults (Study 7) [see *Indications and Usage (1)*].

Patients Ages 6 to 12 Years Old

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), an 18-item questionnaire with a score range of 0-54 points that measures 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 similar; however, 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 optimization with Adderall XR[®], patients were randomly assigned to continue their optimized 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. Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose using the Swanson, Kotkin, Agler, M.Flynn, and Pelham Department scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures department problems leading to classroom disruptions. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS across the 8 assessments were observed between patients when they received Vyvanse compared to patients when they received placebo (Study 2 in Table 4). The drug effect reached statistical significance from hours 2 to 12 post-dose, but was not significant at 1 hour.

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 optimization with Vyvanse (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue their optimized dose of 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 when they received Vyvanse compared to patients when they received placebo (Study 3 in Table 4, Figure 1).

Patients Ages 13 to 17 Years Old

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 1:1:1:1 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)₂. 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).

Adults: Short-Term Treatment

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). 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, cross-over, 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), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. 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).

Adults: Maintenance Treatment

A double-blind, placebo-controlled, randomized withdrawal design study (Study 7) was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV 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 Clinical Global Impression Severity (CGI-S) ≤ 3 and Total Score on the ADHD-RS < 22 . ADHD-RS Total Score is a measure of core symptoms of ADHD. The CGI-S score assesses the clinician's impression of the patient's current illness state and ranges from 1 (not at all ill) to 7 (extremely ill). Patients that maintained treatment response at week 3 of the 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. The efficacy endpoint was the proportion of patients with treatment failure during the double-blind phase. Treatment failure was defined as a $\geq 50\%$ increase (worsening) in the ADHD-RS Total Score and ≥ 2 -point increase in the CGI-S score compared to scores at entry into the double-blind phase (Study 7, Figure 3). Maintenance of efficacy for patients treated with Vyvanse was demonstrated by the significantly lower proportion of patients with treatment failure (9%) compared to patients receiving placebo (75%) at endpoint during the double-blind phase (Figure 3).

Table 4: Summary of Primary Efficacy Results from 1-4 Week Studies of Vyvanse in Children 6-12 Years Old, Adolescents 13 to 17 Years Old, and Adults with ADHD

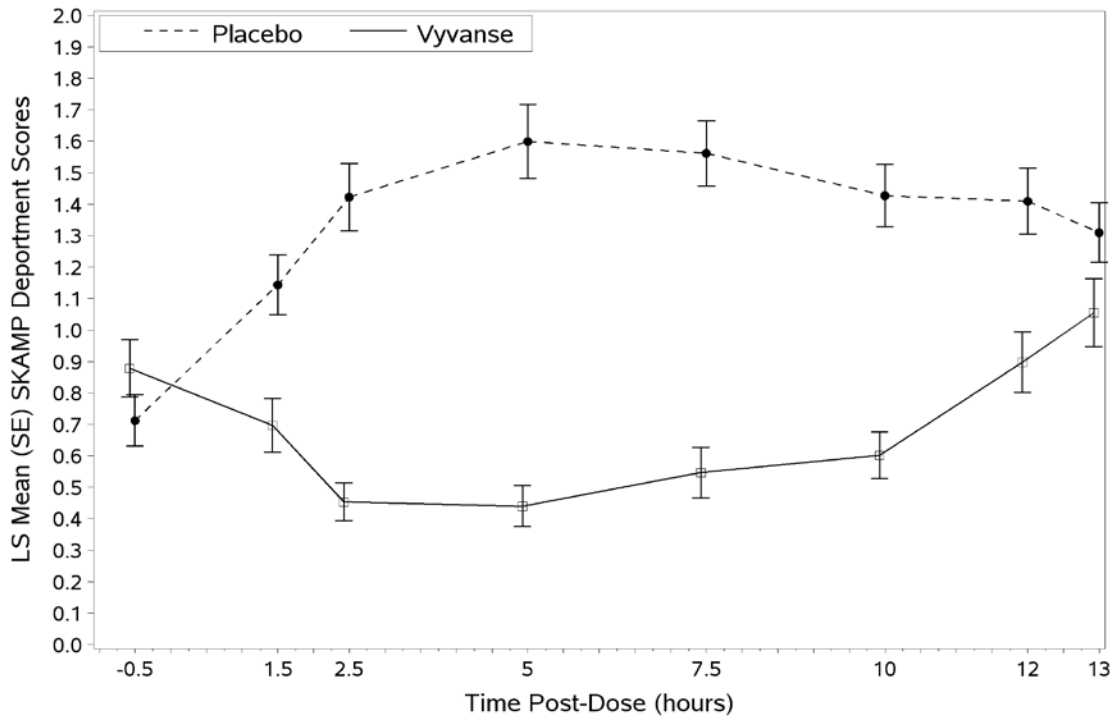
Study No. (Age range)	Primary Endpoint	Measure	Placebo	Vyvanse 30 mg/day	Vyvanse 50 mg/day	Vyvanse 70 mg/day	Vyvanse 30, 50, or 70 mg/day
1 (6 -12 years)	ADHD-RS-IV	Mean Baseline Score	42.4	43.2	43.3	45.1	-
		LS Mean difference from Placebo (95% CI) ^a	-	-15.6 (-20.8, -10.4)	-17.2 (-22.3, -12.1)	-20.5 (-25.6, -15.4)	-
2 (6 -12 years)	Average SKAMP-DS	Mean Pre-dose Score ^b	-	-	-	-	-
		LS Mean difference from Placebo (95% CI) ^a	-	-	-	-	-0.9 (-1.1, -0.7)
3 (6 -12 years)	Average SKAMP-DS	Mean Pre-dose Score	0.7	-	-	-	0.9
		LS Mean difference from Placebo (95% CI) ^a	-	-	-	-	-0.7 (-0.9, -0.6)
4 (13 -17 years)	ADHD-RS-IV	Mean Baseline Score	38.5	38.3	37.3	37.0	-
		LS Mean difference from Placebo (95% CI) ^a	-	-5.5 (-9.7, -1.3)	-8.3 (-12.5, -4.1)	-7.9 (-12.1, -3.8)	-
5 (18 -55 years)	ADHD-RS-IV	Mean Baseline Score	39.4	40.5	40.8	41.0	-
		LS Mean difference from Placebo (95% CI) ^a	-	-8.0 (-12.1, -3.9)	-9.2 (-13.2, -5.1)	-10.4 (-14.5, -6.3)	-
6 (18 -55 years)	Average PERMP	Mean Pre-dose Score	261.4	-	-	-	260.1
		LS Mean difference from Placebo (95% CI) ^a	-	-	-	-	23.4 (15.6, 31.2)

^a Difference (drug – placebo) in Least Squares 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.

^b Pre-dose SKAMP-DS was not collected

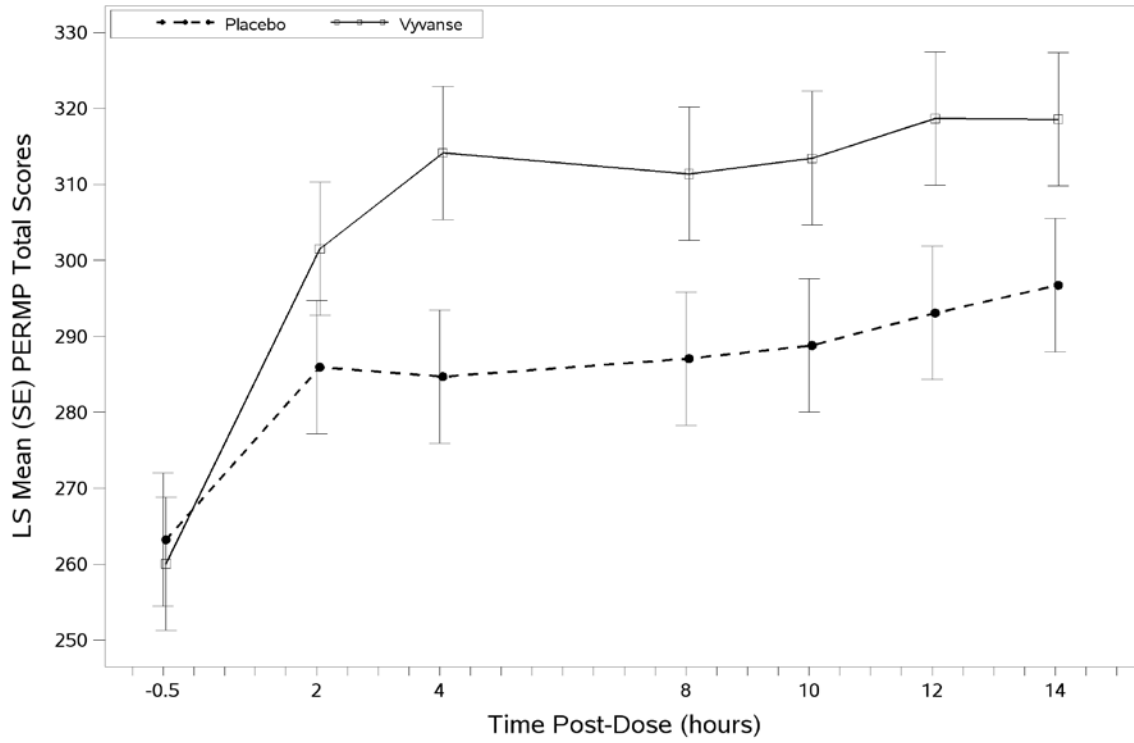
CI: Confidence interval

Figure 1 LS Mean SKAMP Department Subscale Score by Treatment and Time-point for Children Ages 6 to 12 with ADHD after 1 Week of Double Blind Treatment (Study 3)



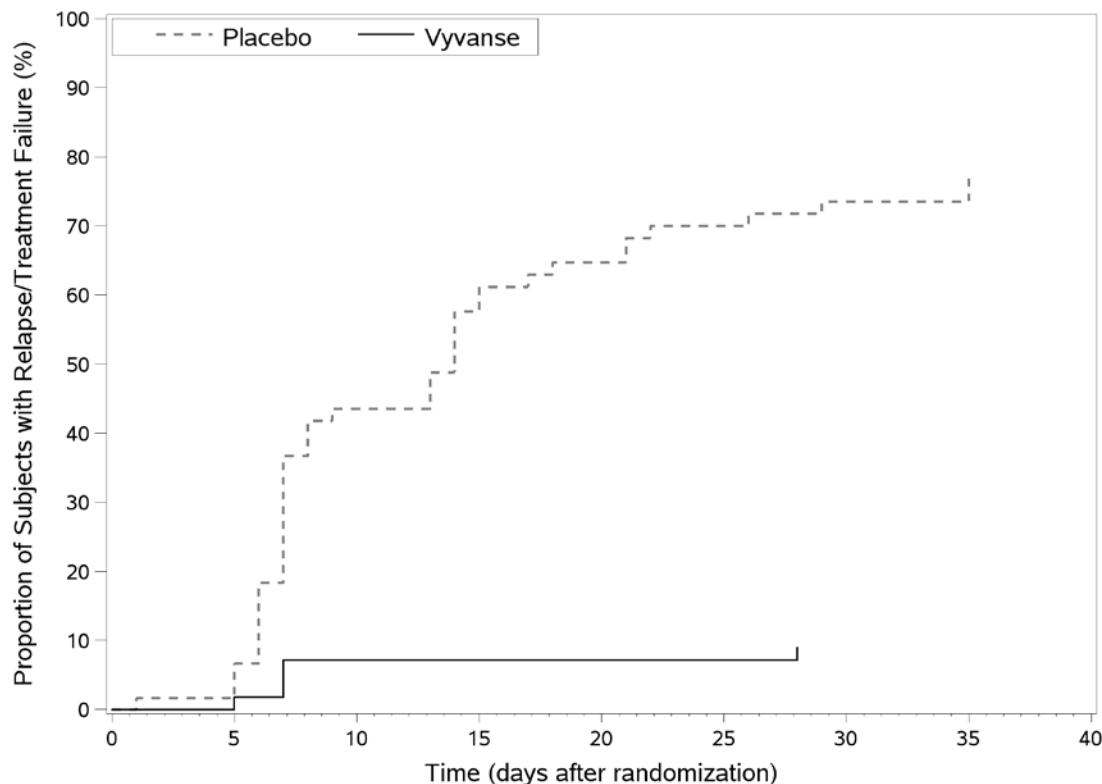
Higher score on the SKAMP-Department scale indicates more severe symptoms

Figure 2 LS Mean (SE) PERMP Total Score at by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double Blind Treatment (Study 6)



Higher score on the PERMP scale indicates less severe symptoms.

Figure 3 Kaplan-Meier Estimation of Time to Treatment Failure in Adults with ADHD (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

16.2 Storage and Handling

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]

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired Vyvanse by a medicine take-back program.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Information on Medication Guide

Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Vyvanse and counsel them in its appropriate use. A patient Medication Guide is available for Vyvanse. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Give patients the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is attached to the prescribing information.

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients and their caregivers that Vyvanse is a controlled substance and it can be abused and lead to dependence and not to give Vyvanse to anyone else [see *Drug Abuse and Dependence (9.1, 9.2, and 9.3)*]. Advise patients to store Vyvanse in a safe place, preferably locked, to prevent abuse. Advise patients to dispose of remaining, unused, or expired Vyvanse by a medicine take-back program.

Serious Cardiovascular Risks

Advise patients, caregivers, and family members that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with Vyvanse use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [see *Warnings and Precautions (5.2)*].

Hypertension and Tachycardia

Instruct patients that Vyvanse can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects.

Psychiatric Risks

Advise patients that Vyvanse at recommended doses may cause psychotic or manic symptoms even in patients without prior history of psychotic symptoms or mania [see *Warnings and Precautions (5.4)*].

Suppression of Growth

Advise patients, family members, and caregivers that Vyvanse may cause slowing of growth including weight loss [see *Warnings and Precautions (5.5)*].

Pregnancy

Instruct patients to tell their healthcare provider if they become pregnant or intend to become pregnant during Vyvanse treatment. Advise patients of the potential fetal effects from the use of Vyvanse during pregnancy [*see Use in Specific Populations (8.1)*].

Nursing

Advise patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed an infant [*see Use in Specific Populations (8.3)*].

Impairment in Ability to Operate Machinery or Vehicles

Advise patients that Vyvanse may impair their ability to engage in potentially dangerous activities such as operating machinery or vehicles. Instruct patients to find out how Vyvanse will affect them before engaging in potentially dangerous activities.

For the Pharmacist

Dispense a Medication Guide to patients receiving a Vyvanse prescription.

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

Made in USA

For more information call 1-800-828-2088

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