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VYVANSE

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, 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, 5.2), and Drug Abuse and Dependence (9.2, 9.3)].*

NAME OF THE MEDICINAL PRODUCT

Vyvanse 30 mg
Vyvanse 50 mg
Vyvanse 70 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is Lisdexamfetamine Dismesylate

For the full list of excipients, see section "DESCRIPTION" below.

PHARMACEUTICAL FORM

Capsules

1 INDICATIONS AND USAGE

Vyvanse is a central nervous system (CNS) stimulant indicated for

- the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 years and above.
- the treatment of Moderate to Severe Binge Eating Disorder (BED) for patients over 18 years.

Limitation of Use:

VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic

drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pre-treatment Screening

Prior to treating children, adolescents, and adults with CNS stimulants, including VYVANSE, 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)]*.

2.2 General Instructions for Use

Take VYVANSE by mouth 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:

- Swallow VYVANSE capsules whole, or
- Open capsules, empty and mix the entire contents with yogurt, water, or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder. The contents should be mixed until completely dispersed. Consume the entire mixture **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 or container once the mixture is consumed. Do not take anything less than one capsule per day, and a single capsule should not be divided.

2.3 Dosage for Treatment of ADHD

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 *[see Clinical Studies (14.1)]*.

2.4 Dosage for Treatment of Moderate to Severe BED in Adults

The recommended starting dose is 30 mg/day to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 to 70 mg/day. The maximum dose is 70 mg/day *[see Clinical Studies (14.2)]*. Discontinue VYVANSE if binge eating does not improve.

2.5 Dosage in Patients with Renal Impairment

In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m^2), the maximum recommended dose is 30 mg/day *[see Use in Specific Populations (8.6)]*.

2.6 Dosage Modifications due to Drug Interactions

Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust VYVANSE dosage accordingly *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

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

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

and 50 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)]*.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, 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.

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 (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

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 VYVANSE. 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 with ADHD, 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)]*.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including VYVANSE, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see Drug Interactions (7.1)]*. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism *[see Clinical Pharmacology 12.3]*. The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to the active metabolite of VYVANSE (dextroamphetamine). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (7.1)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Concomitant use of VYVANSE with MAOI drugs is contraindicated *[see Contraindications (4)]*.

Discontinue treatment with VYVANSE and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. Concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors should be used only if the potential benefit justifies the potential risk. If clinically warranted, consider initiating VYVANSE with lower doses, monitoring patients for the emergence of serotonin syndrome during drug initiation or titration, and informing patients of the increased risk for serotonin syndrome.

6 ADVERSE REACTIONS

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

- labeling Known hypersensitivity to amphetamine products or other ingredients of VYVANSE *[see Contraindications (4)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*
- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- 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 *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[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 practice.

Attention Deficit Hyperactivity Disorder

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 (14.1)]*.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD 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 7), 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 ≥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 with ADHD 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 7) 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) with ADHD 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 with ADHD 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 with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4- Week Clinical Trial (Study 7)

	VYVANSE (n=358)	**Placebo (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%

Increased Blood Pressure	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Decreased Weight	3%	0%
Dyspnea	2%	0%
Increased Heart Rate	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 with ADHD

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 60.9 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 with ADHD

In the controlled adult trial (Study 7), 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.

Binge Eating Disorder

The safety data in this section is based on data from two 12 week parallel group, flexible-dose, placebo-controlled studies in adults with BED *[see Clinical Studies 14.2]*. Patients with cardiovascular risk factors other than obesity and smoking were excluded.

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials

In controlled trials of patients ages 18 to 55 years, 5.1% (19/373) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of VYVANSE-treated patients.

The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.

Adverse reactions reported in the pooled controlled trials in adult patients (Study 11 and 12) treated with VYVANSE or placebo are presented in Table 4 below.

Table 4 Adverse Reactions Reported by 2% or More of Adult Patients with BED Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in 12-Week Clinical Trials (Study 11 and 12)

	VYVANSE (N=373)	Placebo (N=372)
Dry Mouth	36%	7%
Insomnia[1]	20%	8%
Decreased Appetite	8%	2%
Increased Heart Rate[2]	7%	1%
Feeling Jittery	6%	1%
Constipation	6%	1%
Anxiety	5%	1%
Diarrhea	4%	2%
Decreased Weight	4%	0%
Hyperhidrosis	4%	0%
Vomiting	2%	1%
Gastroenteritis	2%	1%
Paresthesia	2%	1%
Pruritus	2%	1%
Upper Abdominal Pain	2%	0%
Energy Increased	2%	0%
Urinary Tract Infection	2%	0%
Nightmare	2%	0%
Restlessness	2%	0%
Oropharyngeal Pain	2%	0%

[1] Includes all preferred terms containing the word "insomnia."
[2] Includes the preferred terms heart rate increased and tachycardia.

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, dysgeusia, tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh. gov.il

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 5 Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer VYVANSE during or within 14 days following the administration of MAOI [see *Contraindications (4)*].
Examples	selegiline, isocarboxazid, phenelzine, tranylcypromine
Serotonergic Drugs	
Clinical Impact	The concomitant use of VYVANSE and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during VYVANSE initiation or dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.7)]*.
Examples	selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of VYVANSE and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of VYVANSE compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during VYVANSE initiation and after a dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the CYP2D6 inhibitor *[see Warnings and Precautions (5.7) and Overdosage (10)]*.
Examples	paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir
Alkalinizing Agents	
Clinical Impact	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of VYVANSE and urinary alkalinizing agents should be avoided.
Examples	Urinary alkalinizing agents (e.g. acetazolamide, some thiazides).
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.

Examples	Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).
Tricyclic Antidepressants	
	May enhance the activity of tricyclic or sympathomimetic agents

Clinical Impact	causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.
Examples	desipramine, protriptyline

7.2 Drugs Having No Clinically Important Interactions with VYVANSE

From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered *[see Clinical Pharmacology (12.3)]*.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lansoprazole, clobazam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when VYVANSE is co-administered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data from published literature and postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines *[see Clinical Considerations]*. In animal reproduction studies, lisdexamfetamine dimesylate (a prodrug of d-amphetamine) had no effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis. Pre- and postnatal studies were not conducted with lisdexamfetamine dimesylate. However, amphetamine (d- to l- ratio of 3:1) administration to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as VYVANSE, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. 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.

Data

Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryo-fetal 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 (MRHD) of 70 mg/day given to adolescents, on a mg/m^2 body surface area basis.

A study was conducted with amphetamine (d- to l- enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. These doses are approximately 0.8, 2, and 4 times the MRHD of amphetamine (d- to l- ratio of 3:1) for adolescents of 20 mg/day, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies from the literature 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.

8.2 Lactation

Risk Summary

Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d-or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with VYVANSE.

8.4 Pediatric Use

ADHD

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 (14.1)]*. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

BED

Safety and effectiveness in patients less than 18 years of age 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/m^2 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^2 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 and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have 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.

8.6 Renal Impairment

Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR < 15 mL/min/1.73 m^2) patients is 30 mg/day *[see Clinical Pharmacology (12.3)]*.

Lisdexamfetamine and d-amphetamine are not dialyzable.

8.7 Gender

No dosage adjustment of VYVANSE is necessary on the basis of gender *[see Clinical Pharmacology (12.3)]*.

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

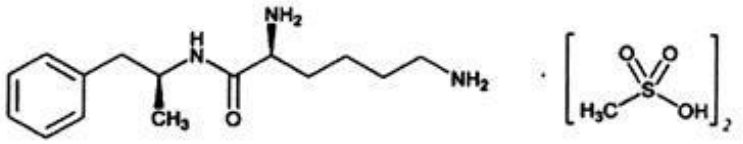
Consult with a Certified Poison Control Center for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of 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. Serotonin syndrome has been reported with amphetamine use, including VYVANSE. 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.

Lisdexamfetamine and d-amphetamine are not dialyzable.

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*-[(1*S*)- 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 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine).

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. The exact mode of therapeutic action in ADHD and BED is not known.

12.2 Pharmacodynamics

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 after oral administration of lisdexamfetamine dimesylate have been conducted in healthy adult (capsule and chewable tablet formulations) and pediatric (6 to 12 years) patients with ADHD (capsule formulation). After single dose administration of lisdexamfetamine dimesylate, pharmacokinetics of dextroamphetamine was found to be linear between 30 mg and 70 mg in a pediatric study, and between 50 mg and 250 mg in an adult study. Dextroamphetamine pharmacokinetic parameters following administration of lisdexamfetamine dimesylate in adults exhibited low inter-subject (<25%) and intra-subject (<8%) variability. There is no accumulation of lisdexamfetamine and dextroamphetamine at steady state in healthy adults.

Safety and efficacy have not been studied above the maximum recommended dose of 70 mg.

Absorption

Capsule formulation

Following single-dose oral administration of VYVANSE capsule (30 mg, 50 mg, or 70 mg) in patients ages 6 to 12 years with ADHD under fasted conditions, T_{max} of lisdexamfetamine and dextroamphetamine was reached at approximately 1 hour and 3.5 hour post dose, respectively. Weight/Dose normalized AUC and C_{max} values were the same in pediatric patients ages 6 to 12 years as the adults following single doses of 30 mg to 70 mg VYVANSE capsule.

Food effect on capsule formulation

Neither food (a high fat meal or yogurt) nor orange juice affects the observed AUC and C_{max} of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of VYVANSE capsules. Food prolongs T_{max} by approximately 1 hour (from 3.8 hour at fasted state to 4.7 hour after a high fat meal or to

4.2 hour with yogurt). After an 8-hour fast, the AUC for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Elimination

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. The mean plasma elimination half- life of dextroamphetamine was about 12 hours after oral administration of lisdexamfetamine dimesylate.

Metabolism

Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells after oral administration, lisdexamfetamine.

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.

Excretion

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.

Specific Populations

Exposures of dextroamphetamine in specific populations are summarized in Figure 1.

Figure 1: Specific Populations*:

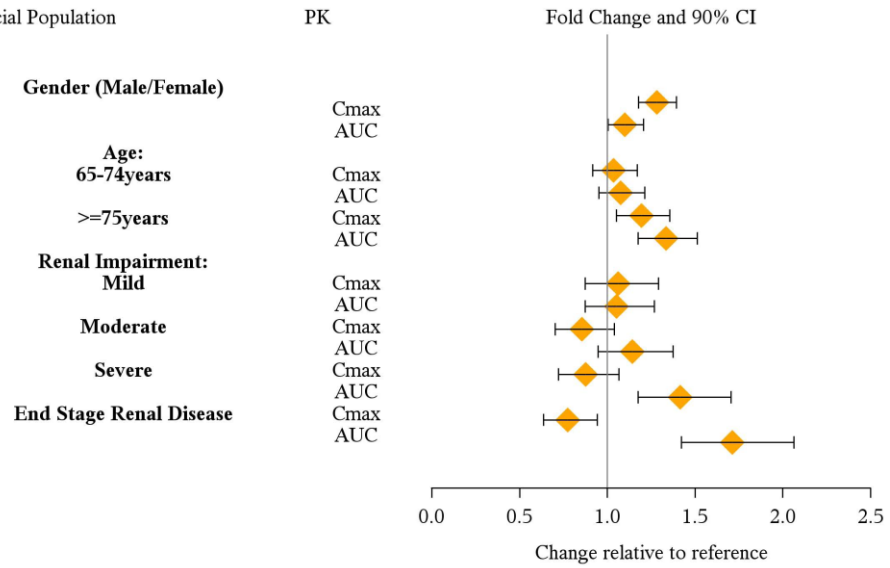
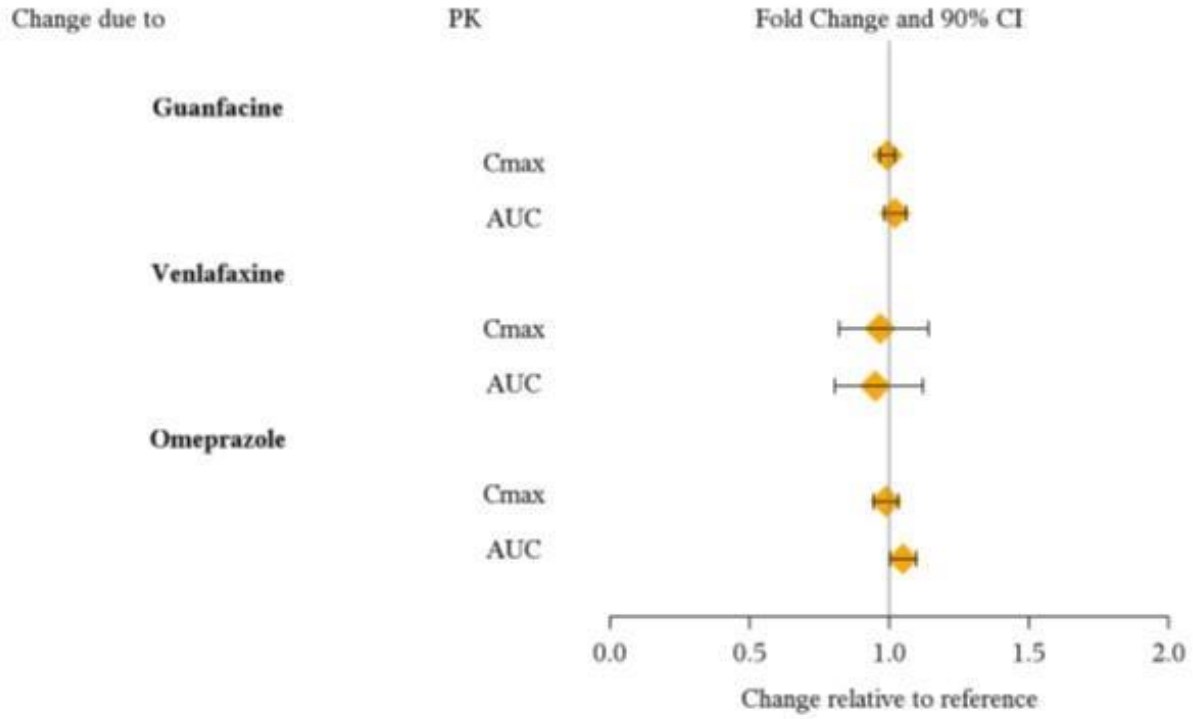


*Figure 1 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

Drug Interaction Studies

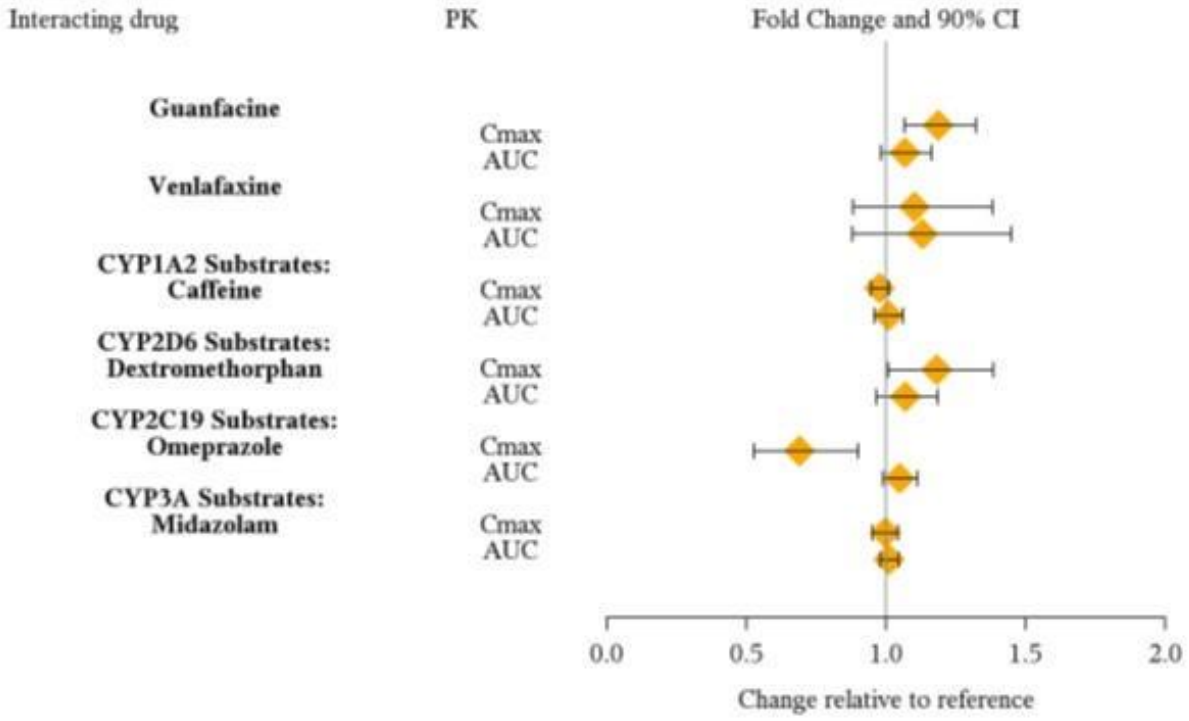
Effects of other drugs on the exposures of dextroamphetamine are summarized in Figure 2.

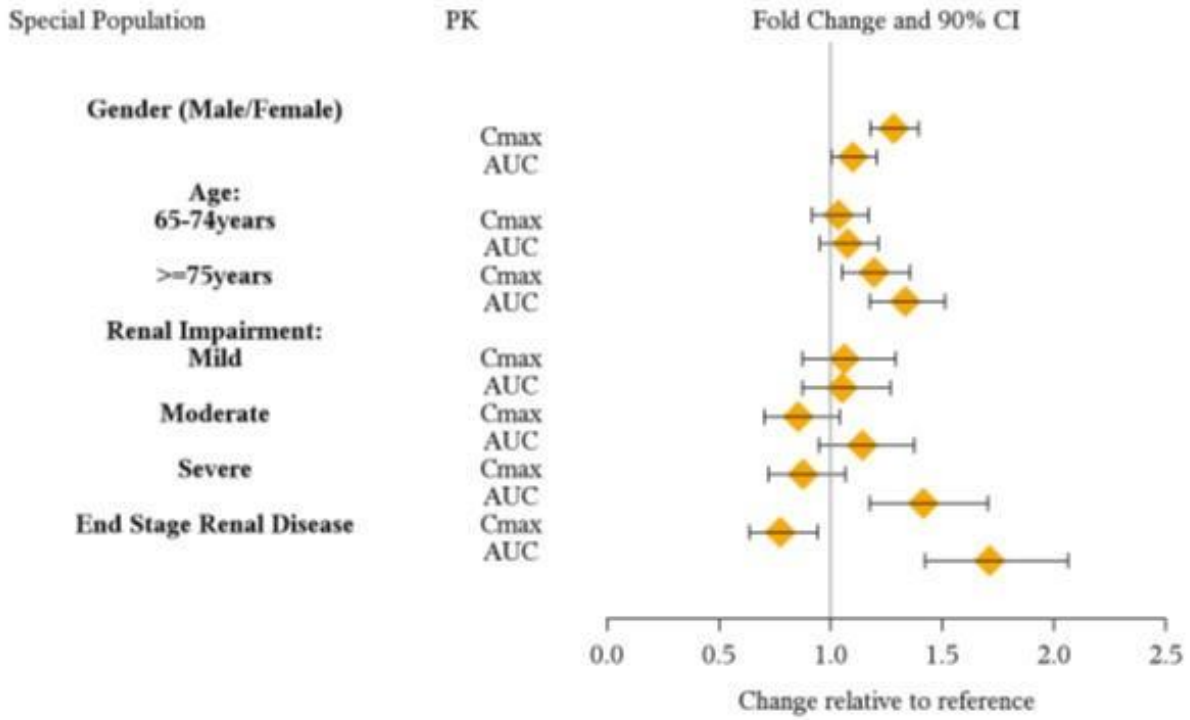
Figure 2: Effect of Other Drugs on VYVANSE:



The effects of VYVANSE on the exposures of other drugs are summarized in Figure 3.

Figure 3 Effect of VYVANSE on Other Drugs:





* Figure 3 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d- amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55- 64 years as the reference.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and 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

Efficacy of VYVANSE in the treatment of ADHD has been established in the following trials:

- Three short-term trials in children (6 to 12 years, Studies 1, 2, 3)

- One short-term trial in adolescents (13 to 17 years, Study 4)
- One short-term trial in children and adolescents (6 to 17 years, Study 5)
- Two short-term trials in adults (18 to 55 years, Studies 7, 8)
- Two randomized withdrawal trials in children and adolescents (6 to 17 years, Study 6), and adults (18 to 55 years, Study 9)

Efficacy of VYVANSE in the treatment of moderate to severe BED in adults has been established in the following trials:

- One randomized trial in adults (18 to 55 years, Study 10)
- Two short-term trials in adults (18 to 55 years, Studies 11 and 12)
- One randomized withdrawal study in adults (18 to 55 years, Study 13)

14.1 Attention Deficit Hyperactivity Disorder (ADHD)

Patients Ages 6 to 12 Years Old with ADHD

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 7). 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 Deportment scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures deportment 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 7). 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-Deportment 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 7, Figure 4).

Patients Ages 13 to 17 Years Old with ADHD

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). 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 7).

Patients Ages 6 to 17 Years Old: Short-Term Treatment in ADHD

A double-blind, randomized, placebo- and active-controlled parallel-group, dose-optimization study (Study 5) was conducted in children and adolescents ages 6 to 17 years (n=336) who met DSM-IV criteria for ADHD. In this eight-week study, patients were randomized to a daily morning dose of VYVANSE (30, 50 or 70mg/day), an active control, or placebo (1:1:1). The study consisted of a Screening and Washout Period (up to 42 days), a 7-week Double-blind Evaluation Period (consisting of a 4-week Dose-Optimization Period followed by a 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. During the Dose Optimization Period, subjects were titrated until an optimal dose, based on tolerability and investigator's judgment, was reached. VYVANSE showed significantly greater efficacy than placebo. The placebo-adjusted mean reduction from baseline in the ADHD-RS-IV total score was 18.6. Subjects on VYVANSE also showed greater improvement on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to subjects on placebo (Study 5 in Table 7).

Patients Ages 6 to 17 Years Old: Maintenance Treatment in ADHD

Maintenance of Efficacy Study (Study 6) - A double-blind, placebo-controlled, randomized withdrawal study was conducted in children and adolescents ages 6 to 17 (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label VYVANSE for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and Total Score on the ADHD-RS ≤22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized to ongoing treatment with the same dose of VYVANSE (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. A significantly lower proportion of treatment failures occurred among VYVANSE subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase. Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5).

Adults: Short-Term Treatment in ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 7) 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 7 in Table 7).

The second study was a multi-center, randomized, double-blind, placebo-controlled, cross-over, modified analog classroom study (Study 8) 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 8 in Table 7 , Figure 6).

Adults: Maintenance Treatment in ADHD

A double-blind, placebo-controlled, randomized withdrawal design study (Study 9) 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 ≥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. 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 (Study 9, Figure 7).

Table 7: Summary of Primary Efficacy Results from Short-term Studies of VYVANSE in Children, Adolescents, and Adults with ADHD

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1 (6 - 12 years)	ADHD-RS-IV	VYVANSE (30 mg/day)†	43.2 (6.7)	-21.8 (1.6)	-15.6 (-19.9, -11.2)
		VYVANSE (50 mg/day)†	43.3 (6.7)	-23.4 (1.6)	-17.2 (-21.5, -12.9)
		VYVANSE (70 mg/day)†	45.1(6.8)	-26.7 (1.5)	-20.5 (-24.8, -16.2)
		Placebo	42.4 (7.1)	-6.2 (1.6)	--

Study 2 (6 - 12 years)	Average SKAMP-DS	VYVANSE (30, 50 or 70 mg/day)†	-- ‡	0.8 (0.1)§	-0.9 (-1.1, -0.7)
		Placebo	-- ‡	1.7 (0.1)§	--
Study 3 (6 - 12 years)	Average SKAMP-DS	VYVANSE (30, 50 or 70 mg/day)†	0.9 (1.0)¶	0.7 (0.1)§	-0.7 (-0.9, -0.6)
		Placebo	0.7 (0.9)¶	1.4 (0.1)§	--
Study 4 (13 - 17 years)	ADHD-RS-IV	VYVANSE (30 mg/day)†	38.3 (6.7)	-18.3 (1.2)	-5.5 (-9.0, -2.0)
		VYVANSE (50 mg/day)†	37.3 (6.3)	-21.1 (1.3)	-8.3 (-11.8, -4.8)
		VYVANSE (70 mg/day)†	37.0 (7.3)	-20.7 (1.3)	-7.9 (-11.4, -4.5)
		Placebo	38.5 (7.1)	-12.8 (1.2)	--
Study 5 (6 - 17 years)	ADHD-RS-IV	VYVANSE (30, 50 or 70 mg/day)†	40.7 (7.3)	-24.3 (1.2)	-18.6 (-21.5, -15.7)
		Placebo	41.0 (7.1)	-5.7 (1.1)	--
Study 7 (18 - 55 years)	ADHD-RS-IV	VYVANSE (30 mg/day)†	40.5 (6.2)	-16.2 (1.1)	-8.0 (-11.5, -4.6)
		VYVANSE (50 mg/day)†	40.8 (7.3)	-17.4 (1.0)	-9.2 (-12.6, -5.7)
		VYVANSE (70 mg/day)†	41.0 (6.0)	-18.6 (1.0)	-10.4 (-13.9, -6.9)
		Placebo	39.4 (6.4)	-8.2 (1.4)	--
Study 8 (18 - 55 years)	Average PERMP	VYVANSE (30, 50 or 70 mg/day)†	260.1 (86.2)¶	312.9 (8.6)§	23.4 (15.6, 31.2)
		Placebo	261.4 (75.0)¶	289.5 (8.6)§	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

* Difference (drug minus placebo) in least- squares mean change from baseline.

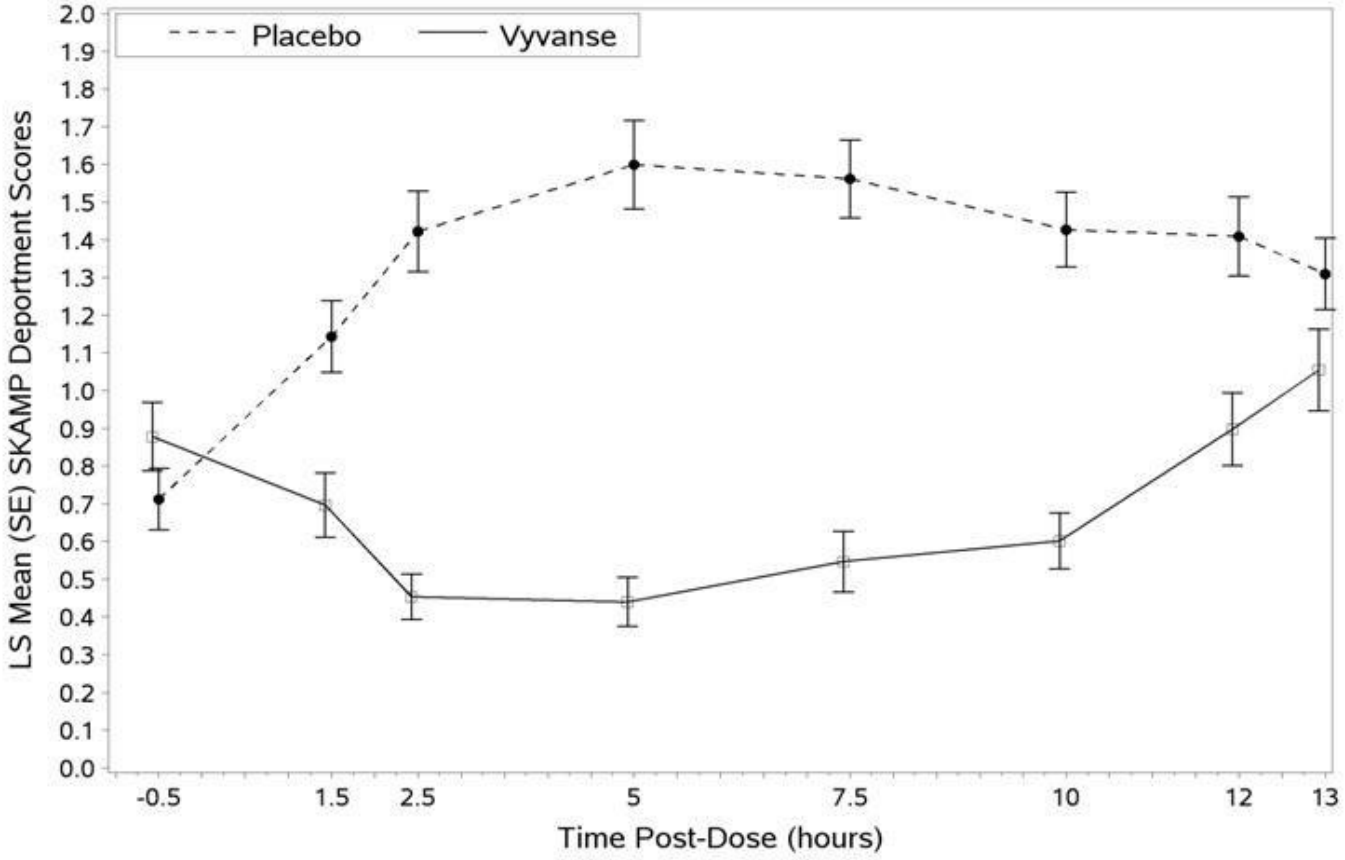
† Doses statistically significantly superior to placebo.

‡ Pre- dose SKAMP- DS was not collected.

§ LS Mean for SKAMP- DS (Study 2 and 3) or PERMP (Study 8) is post- dose average score over all sessions of the treatment day, rather than change from baseline.

¶ Pre- dose SKAMP- DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.

Figure 4 LS Mean SKAMP Deportment 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-Deportment scale indicates more severe symptoms

Figure 5 Kaplan-Meier Estimated Proportion of Patients with Treatment Failure for Children and Adolescent Ages 6-17 (Study 6)

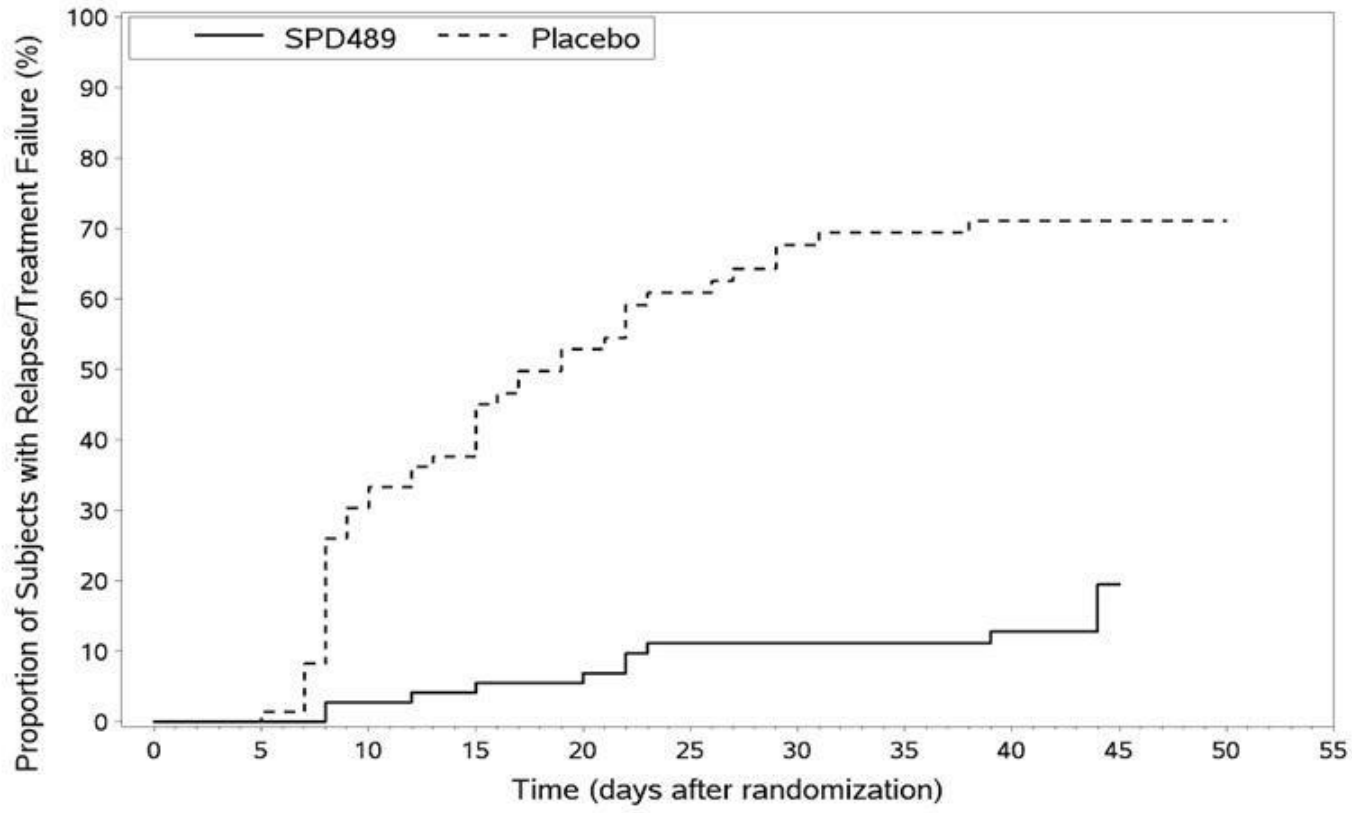
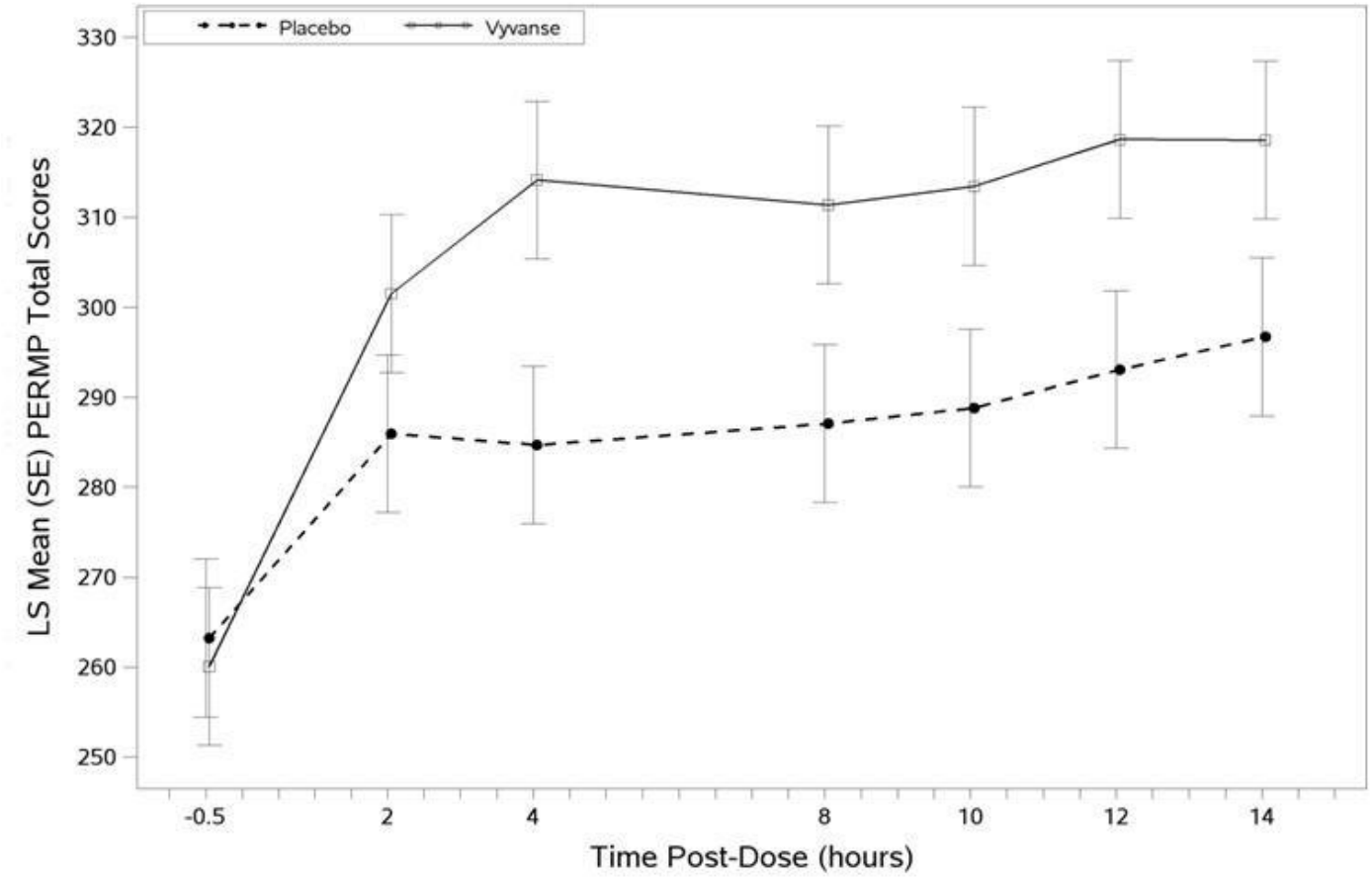
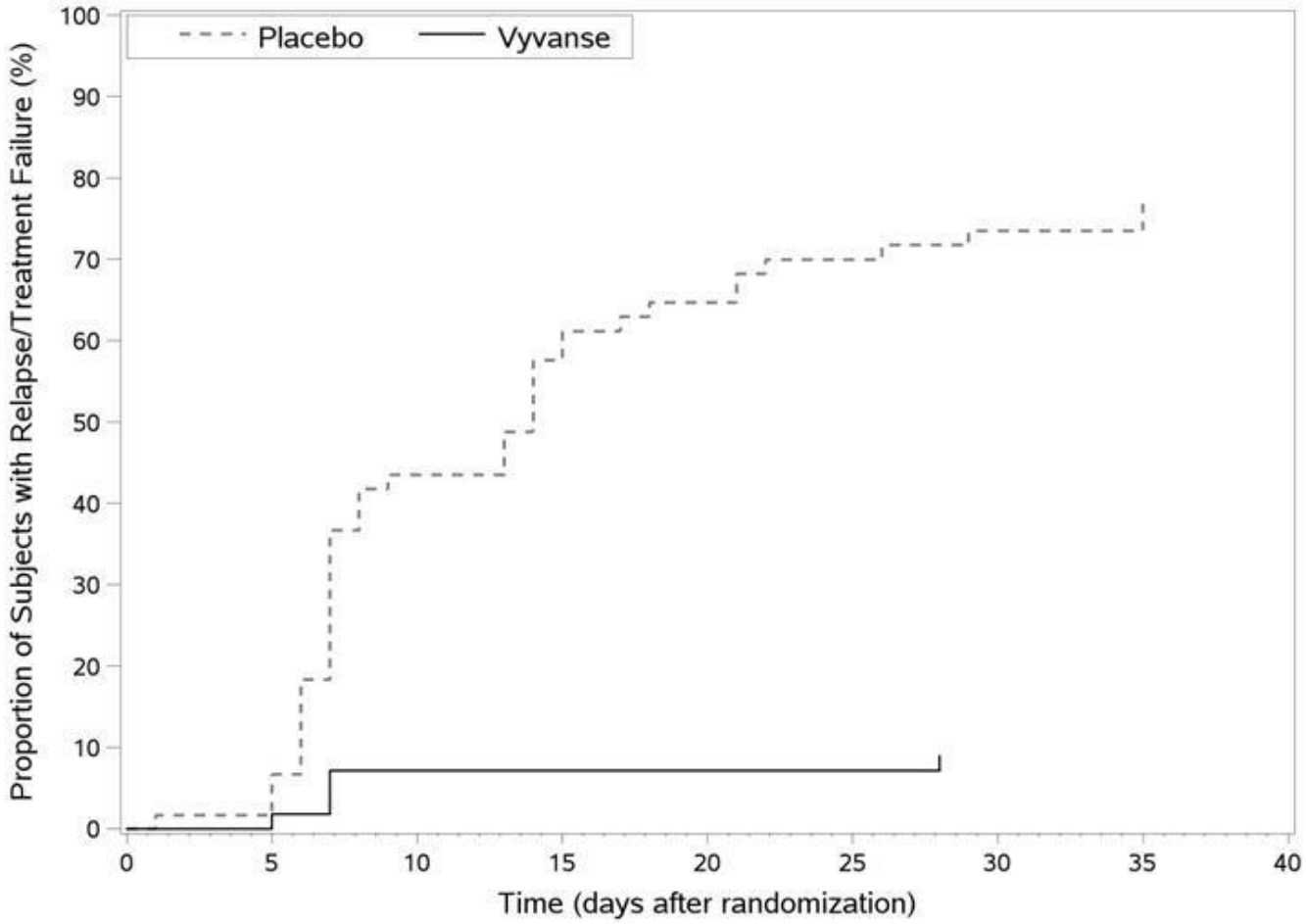


Figure 6 LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

Figure 7 Kaplan-Meier Estimated Proportion of Subjects with Relapse in Adults with ADHD (Study 9)



14.2 Binge Eating Disorder (BED)

A phase 2 study evaluated the efficacy of VYVANSE 30, 50 and 70 mg/day compared to placebo in reducing the number of binge days/week in adults with at least moderate to severe BED. This randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study (Study 10) consisted of an 11-week double-blind treatment period (3 weeks of forced-dose titration followed by 8 weeks of dose maintenance). VYVANSE 30 mg/day was not statistically different from placebo on the primary endpoint. The 50 and 70 mg/day doses were statistically superior to placebo on the primary endpoint.

The efficacy of VYVANSE in the treatment of BED was demonstrated in two 12-week randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization studies (Study 11 and Study 12) in adults aged 18-55 years (Study 11: N=374, Study 12: N=350) with moderate to severe BED. A diagnosis of BED was confirmed using DSM-IV criteria for BED. Severity of BED was determined based on having at least 3 binge days per week for 2 weeks prior to the baseline visit and on having a Clinical Global Impression Severity (CGI-S) score of ≥4 at the baseline visit. For both studies, a binge day was defined as a day with at least 1 binge episode, as determined from the subject's daily binge diary.

Both 12-week studies consisted of a 4-week dose-optimization period and an 8-week dose-maintenance period. During dose-optimization, subjects assigned to VYVANSE began treatment at the titration dose of 30 mg/day and, after 1 week of treatment, were subsequently titrated to 50mg/day. Additional increases to 70 mg/day were made as tolerated and clinically indicated. Following the dose-optimization period, subjects continued on their optimized dose for the duration of the dose-maintenance period.

The primary efficacy outcome for the two studies was defined as the change from baseline at Week 12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit. Subjects from both studies on VYVANSE had a statistically significantly greater reduction from baseline in mean number of binge days per week at Week 12. In addition, subjects on VYVANSE showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score.

Table 8: Summary of Primary Efficacy Results in BED

Study Number	Treatment Group	Primary Efficacy Measure: Binge Days per Week at Week 12		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 11	VYVANSE (50 or 70 mg/day)†	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study 12	VYVANSE (50 or 70 mg/day)†	4.66 (1.27)	-3.92 (0.14)	-1.66 (-2.04, -1.28)
	Placebo	4.82 (1.42)	-2.26 (0.14)	--

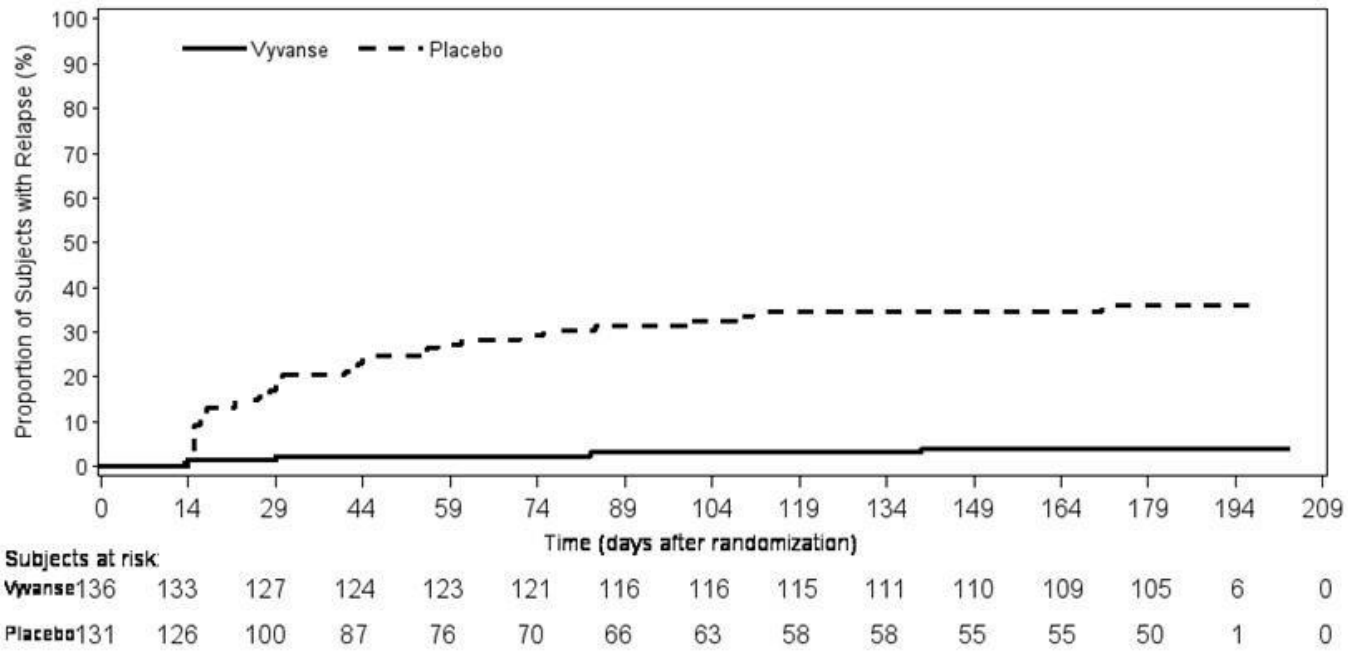
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

* Difference (drug minus placebo) in least- squares mean change from baseline.

† Doses statistically significantly superior to placebo.

A double-blind, placebo controlled, randomized withdrawal design study (Study 13) was conducted to evaluate maintenance of efficacy based on time to relapse between VYVANSE and placebo in adults aged 18 to 55 (N=267) with moderate to severe BED. In this longer-term study patients who had responded to VYVANSE in the preceding 12-week open-label treatment phase were randomized to continuation of VYVANSE or placebo for up to 26 weeks of observation for relapse. Response in the open-label phase was defined as 1 or fewer binge days each week for four consecutive weeks prior to the last visit at the end of the 12-week open-label phase and a CGI-S score of 2 or less at the same visit. Relapse during the double-blind phase was defined as having 2 or more binge days each week for two consecutive weeks (14 days) prior to any visit and having an increase in CGI-S score of 2 or more points compared to the randomized-withdrawal baseline. Maintenance of efficacy for patients who had an initial response during the open-label period and then continued on VYVANSE during the 26-week double-blind randomized-withdrawal phase was demonstrated with VYVANSE being superior over placebo as measured by time to relapse.

Figure 8 Kaplan-Meier Estimated Proportion of Subjects with Relapse in Adults with BED (Study 13)



Examination of population subgroups based on age (there were no patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness in the treatment of BED.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 28,30 or 100,

VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 28, 30 or 100,

VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 28,30 or 100,

16.2 Storage and Handling

Dispense in a tight, light-resistant container .

Do not store above 25°C.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. .

Manufactured by Shire Pharmaceutical Contracts Ltd.,
Kingdom Street 1
London ,W2 6BD
United Kingdom

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Registration number

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Vyvanse 50 mg: 153-20-34001-00

Vyvanse 70 mg: 153-21-34000-00