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

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

- **CNS stimulants, including VYVANSE, other amphetamine-containing products, and methylphenidate have a high potential for abuse and dependence (5.1, 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----------

Indications and Usage (1)	7/2021
Warnings and Precautions (5.5)	7/2021

----------INDICATIONS AND USAGE----------

VYVANSE is a central nervous system (CNS) stimulant indicated for the treatment of (1):

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older
- Moderate to severe binge eating disorder (BED) in adults

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older (8.4)
- VYVANSE is not indicated 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 (5.2)

----------DOSAGE AND ADMINISTRATION----------

Indicated Population	Initial Dose	Titration Schedule	Recommended Dose	Maximum Dose
ADHD (Adults and pediatric patients 6 years and older) (2.2)	30 mg every morning	10 mg or 20 mg weekly	30 mg to 70 mg per day	70 mg per day
BED (Adults) (2.3)	30 mg every morning	20 mg weekly	50 mg to 70 mg per day	70 mg per day

- Prior to treatment, assess for presence of cardiac disease (2.4)
- Severe renal impairment: Maximum dose is 50 mg/day (2.5)
- End stage renal disease (ESRD): Maximum dose is 30 mg/day (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)
- Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 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 has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been 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)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with stimulants (5.6)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue VYVANSE and initiate supportive treatment (4, 5.7, 10)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in pediatric patients ages 6 to 17 years, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

Most common adverse reactions (incidence ≥ 5% and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust VYVANSE dosage accordingly (2.6, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy*: May cause fetal harm (8.1)
- *Lactation:* Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including VYVANSE, other amphetamine-containing products, and methylphenidate, 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) in adults and pediatric patients 6 years and older *[see Clinical Studies (14.1)]*
- Moderate to severe binge eating disorder (BED) in adults *[see Clinical Studies (14.2)]*.

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older *[see Use in Specific Populations (8.4)]*.
- 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 patients 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)]*.

2.2 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:

Information for VYVANSE capsules:

- 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.

Information for VYVANSE chewable tablets:

- VYVANSE chewable tablets must be chewed thoroughly before swallowing.

VYVANSE capsules can be substituted with VYVANSE chewable tablets on a unit per unit/mg per mg basis (for example, 30 mg capsules for 30 mg chewable tablet) *[see Clinical Pharmacology (12.3)]*.

Do not take anything less than one capsule or chewable tablet per day. A single dose should not be divided.

2.3 Dosage for Treatment of ADHD

The recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg once daily in the morning. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum recommended dosage of 70 mg once daily *[see Clinical Studies (14.1)]*.

2.4 Dosage for Treatment of Moderate to Severe BED in Adults

The recommended starting dosage in adults is 30 mg once daily to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 mg to 70 mg once daily. The maximum recommended dosage is 70 mg once daily *[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 dosage should not exceed 50 mg once daily. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m^2), the maximum recommended dosage is 30 mg once daily *[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

*VYVANSE (*lisdexamfetamine dimesylate*) capsules:*

- Capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg)
- 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)

*VYVANSE (*lisdexamfetamine dimesylate*) chewable tablets:*

- Chewable tablets 10 mg: White to off-white round shaped tablet debossed with ‘10’ on one side and ‘S489’ on the other
- Chewable tablets 20 mg: White to off-white hexagonal shaped tablet debossed with ‘20’ on one side and ‘S489’ on the other
- Chewable tablets 30 mg: White to off-white arc triangular shaped tablet debossed with ‘30’ on one side and ‘S489’ on the other
- Chewable tablets 40 mg: White to off-white capsule shaped tablet debossed with ‘40’ on one side and ‘S489’ on the other
- Chewable tablets 50 mg: White to off-white arc square shaped tablet debossed with ‘50’ on one side and ‘S489’ on the other
- Chewable tablets 60 mg: White to off-white arc diamond shaped tablet debossed with ‘60’ on one side and ‘S489’ on the other

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, including VYVANSE, other amphetamine-containing products, and methylphenidate, 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 pediatric patients 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 to 4 mm Hg) and heart rate (mean increase about 3 to 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 (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 patients 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 pediatric 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)]*.

Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. VYVANSE is not approved for use in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

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)]*. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also 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. If concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate VYVANSE with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform 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 Trials 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 controlled parallel-group 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 pediatric patients ages 6 to 12 years (Study 1), 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)]. Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included abdominal pain upper, dry mouth, weight decreased, dizziness, somnolence, logorrhea, chest pain, anger and hypertension.

In the controlled trial in pediatric patients ages 13 to 17 years (Study 4), 3% (7/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%) and insomnia (2/233; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included irritability, dermatillomania, mood swings, and dyspnea.

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 frequently reported adverse reactions (1% or more and twice rate 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%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included palpitations, diarrhea, nausea, decreased appetite, dizziness, agitation, depression, paranoia and restlessness.

Adverse Reactions Occurring at an Incidence of ≥5% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in pediatric patients ages 6 to 17 years, 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), pediatric 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 Pediatric Patients Ages 6 to 12 Years with ADHD Taking VYVANSE and Greater than or Equal to 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	22%	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%
Anorexia	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking VYVANSE and Greater than or Equal to 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%
Palpitations	2%	1%
Anorexia	2%	0%
Tremor	2%	0%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking VYVANSE and Greater than or Equal to 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%
Palpitations	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 pediatric patients 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 pediatric patients ages 6 to 12 years who received VYVANSE over 12 months suggests that consistently medicated pediatric patients (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 pediatric patients 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 pediatric patients 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

pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients ages 7 to 13 years (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 pediatric patients ages 13 to 17 years, 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. Less commonly reported adverse reactions (less than 1% or less than twice rate of placebo) included increased heart rate, headache, abdominal pain upper, dyspnea, rash, insomnia, irritability, feeling jittery and anxiety.

Adverse Reactions Occurring at an Incidence of 5% or More and At Least Twice Placebo Among VYVANSE Treated Patients with BED in Clinical Trials
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 Occurring at an Incidence of 2% or More and At Least Twice Placebo Among VYVANSE Treated Patients with BED in Clinical Trials
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 Greater than or Equal to 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 postapproval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: 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, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

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)]*.
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)]*.
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)]*.
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.
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents 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.

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

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and researchprograms/pregnancyregistry/adhd-medications/.

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 5.5 and 33 times, respectively, the maximum recommended human dose (MRHD) of 70 mg/day given to adults, 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. 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 of VYVANSE have been established in pediatric patients with ADHD ages 6 to 17 years *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

Safety and effectiveness of VYVANSE have not been established in pediatric patients below the age of 6 years.

Safety and efficacy of VYVANSE were evaluated in a double-blind, randomized, parallel-group, placebo-controlled, fixed-dose study in pediatric patients ages 4 to 5 years with ADHD, followed by a 1-year open-label extension study. In these studies, patients experienced elevated rates of adverse reactions, including weight loss, decreased BMI, decreased appetite, insomnia, infections (upper respiratory and nasopharyngitis), irritability, and affect lability.

With the same VYVANSE dose, mean steady state exposure of dextroamphetamine was approximately 44% higher in pediatric patients ages 4 to 5 years compared to the pediatric patients ages 6 to 11 years.

BED
Safety and effectiveness of VYVANSE have not been established in patients less than 18 years of age.

Growth Suppression
Growth should be monitored during treatment with stimulants, including VYVANSE, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5) and 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.

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 amphetamine-containing products, and methylphenidate have a high potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Both abuse and misuse may lead to addiction, and some individuals may develop addiction even when taking VYVANSE as prescribed.

Signs and symptoms of amphetamine 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

Physical Dependence
VYVANSE may produce physical dependence from continued therapy. Physical dependence is a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

Tolerance
VYVANSE may produce tolerance from continued therapy. Tolerance is a state of adaptation in which exposure to a specific dose of a drug results in a reduction of the drug’s desired and/or undesired effects over time.

10 OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) 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.

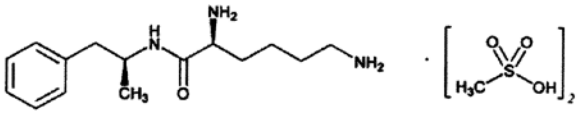
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported 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 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 $C_{15}H_{25}N_3O•(CH_4O_3S)_2$, 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).

Information for VYVANSE capsules:

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.

Information for VYVANSE chewable tablets:

VYVANSE chewable tablets contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, and 34.7 mg of lisdexamfetamine).

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, sucralose, artificial strawberry flavor.

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 (6 to 12 years), 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.

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 hours 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.

Effect of food 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 hours at fasted state to 4.7 hours after a high fat meal or to 4.2 hours 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.

Chewable Tablet formulation
After a single dose administration of 60 mg VYVANSE chewable tablet in healthy subjects under fasted conditions, T_{max} of lisdexamfetamine and dextroamphetamine was reached at approximately 1 hour and 4.4 hours post dose, respectively. Compared to 60 mg VYVANSE capsule, exposure (C_{max} and AUC) to lisdexamfetamine was about 15% lower. The exposure (C_{max} and AUC_{inf}) of dextroamphetamine is similar between VYVANSE chewable tablet and VYVANSE capsule.