PRODUCT MONOGRAPH

VYVANSE®*

lisdexamfetamine dimesylate

Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

Chewable Tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg and 60 mg

Central Nervous System Stimulant

Shire Pharma Canada ULC
22 Adelaide St. West, Suite 3800
Toronto, Ontario
M5H 4E3

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VYVANSE®
lisdexamfetamine dimesylate capsules
lisdexamfetamine dimesylate chewable tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	croscarmellose sodium, magnesium stearate, microcrystalline cellulose and capsule shells which contain edible ink, gelatin, titanium dioxide (E171), and one or more of the following: FD&C Yellow #6 (E110), FD&C Blue #1 (E133), FD&C Red #3 (E127), FDA/E172 Black Iron Oxide, FDA/E172 Yellow Iron Oxide.
	Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	artificial strawberry flavouring, colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, and sucralose.

INDICATIONS AND CLINICAL USE

VYVANSE (lisdexamfetamine dimesylate) capsules and chewable tablets are indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Moderate to Severe Binge Eating Disorder (BED) in adults.

  Recurrent episodes of binge-eating are characterised by:
  - consuming an abnormally large amount of food in a short period of time and sense of lack of control over eating during the episode
  - marked distress about the behavior
  - feeling disgusted or guilty, or eating alone because of embarrassment.

Limitation of Use for BED:

Prescribers should consider that serious cardiovascular (CV) events have been reported with this class of sympathomimetic drugs. The BED clinical trials were not designed to assess CV safety. While there is an accumulation of safety data with VYVANSE use in the ADHD population, this is of limited relevance regarding CV risk in the BED population. Given the higher CV risk

associated with obesity, the BED population may be at a higher risk (see **Warnings and Precautions, Cardiovascular** and **Dosage and Administration**).

The safety and effectiveness of VYVANSE for the treatment of obesity have not been established. 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.

ADHD

A diagnosis of ADHD (DSM-IV-TR®) implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work), and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least six months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least six months (or adult equivalent symptoms): fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, "on the go", excessive talking, blurting answers, can't wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

VYVANSE is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational/vocational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in a patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational/vocational placement is essential in patients with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms and on the level of functional impairment.

Long-term Use
The physician who elects to use VYVANSE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **Dosage and Administration**).

The efficacy of VYVANSE has been evaluated separately in both children and adolescents for up to four weeks, and in adults for up to ten weeks. In a separate controlled trial of a combined population of children and adolescents, the efficacy of VYVANSE has been evaluated for up to seven weeks.

Pediatrics

ADHD
Amphetamines should not be used in pediatric patients with ADHD under six years of age, since safety and efficacy in this age group have not been established.

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

Geriatrics

VYVANSE has not been systematically studied in, and is therefore not indicated for use in, the geriatric population (>65 years of age) (see **Action and Clinical Pharmacology**, **Pharmacokinetics**). Subjects over 55 years of age were excluded from the ADHD and BED clinical trials.

CONTRAINDICATIONS

Cardiovascular
- Moderate to severe hypertension
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease

General
- Hyperthyroidism
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Allergy to amphetamines or to components of VYVANSE or its container
- Glaucoma
- Agitated states
- Patients with a history of drug abuse
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result) (see **Drug Interactions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Amphetamines have a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses that physicians should consider when prescribing this product (see **Cardiovascular, Misuse and Serious Cardiovascular Adverse Events**, and **Dependence Liability** sections below).

General

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. VYVANSE should be used with caution in patients who use other sympathomimetic drugs.

Cardiovascular

Serious cardiovascular events have been reported with the use of sympathomimetic drugs, including VYVANSE, in the ADHD population (as below). Given the higher CV risk associated with obesity, the BED population may be at a higher risk. Prescribers should consider this potential risk when treating BED (see **Indications and Clinical Use, Limitation of Use for BED**).

Limited CV safety information is provided by the BED clinical trials, given the exclusion of higher risk patients (e.g., diabetes, moderate to severe hypertension, and cardiovascular disease; older than 55 years of age) combined with limited patient numbers and limited treatment duration.

As VYVANSE was not developed to the regulatory standard of a weight-loss drug, and is not indicated for weight loss, a post-approval cardiac safety assessment (e.g., a dedicated CV outcome study) is not planned.

i) Misuse and Serious Cardiovascular Adverse Events

The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

ii) Hypertension and Other Cardiovascular Conditions

CNS stimulants such as VYVANSE are known to cause increases in blood pressure and heart rate.

In clinical trials, modest mean increases are seen (about 2-4 mmHg and 3-6 bpm, respectively), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure.

Patients with moderate to severe hypertension, symptomatic CV disease, or advanced arteriosclerosis should not be treated with VYVANSE (see **Contraindications**). Blood pressure

and pulse should be measured prior to initiating treatment, and monitored at appropriate intervals in patients taking VYVANSE, especially patients with hypertension. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Binge Eating Disorder
VYVANSE should be prescribed for the shortest duration that is clinically indicated in order to minimize exposure to CV risk in this population; the risk-benefit profile of the drug for the individual patient should be periodically re-evaluated.

iii) Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents
Sudden death has been reported with sympathomimetic drugs used for ADHD treatment at therapeutic doses in children/adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, sympathomimetic drugs generally should not be used in children/adolescents with known serious structural cardiac abnormalities or other serious cardiac problems (e.g., cardiomyopathy, serious heart rhythm abnormalities), that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs (see **Contraindications**).

Adults
Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see **Contraindications**).

Assessing Cardiovascular Status in Patients Being Treated with Sympathomimetic Medications
Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD or BED should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other sympathomimetic drugs or c) have a family history of sudden/cardiac death. Patients who are being considered for treatment with sympathomimetic medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during sympathomimetic medication treatment for ADHD or BED should undergo a prompt cardiac evaluation.

ADHD Population: Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients (see **Adverse Reactions**). Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including VYVANSE. Patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Children and Adolescents in VYVANSE ADHD Clinical Trials

In a 4-week controlled trial of lisdexamfetamine in children ages 6 to 12 years with ADHD, mean weight loss from baseline to endpoint was -0.9, -1.9, and -2.5lbs, respectively, for patients assigned to receive 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to a 1.0lb weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with four weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received lisdexamfetamine over 12 months suggests that consistently medicated children (i.e., treatment for seven 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 one 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 aged 13 to 17 years with ADHD, mean weight change from baseline to endpoint was -2.7, -4.3, and -4.8lbs, respectively, for patients assigned to receive 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 2.0lb weight gain for patients receiving placebo. Careful follow-up for weight in adolescents aged 13 to 17 years who received lisdexamfetamine over 12 months suggests that consistently medicated adolescents (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 -6.5 over 1 year. The average percentile at baseline (n=265) and 12 months (n=156), were 66.0 and 61.5, respectively.

Stimulant Use in Adolescents and Children with ADHD

Published data for other stimulants report that in children aged 7 to 10 years there is a temporary slowing in growth rate 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 four weeks of therapy was –1.1lbs and –2.8lbs, respectively, for patients receiving 10 mg and 20 mg of amphetamine (*d*- to *l*-enantiomer ratio of 3:1). Higher doses were associated with greater weight loss within the initial four weeks of treatment. Published data are inadequate to determine whether the chronic use of amphetamines in children may be causally associated with suppression of growth.

Carcinogenesis and Mutagenesis, Reproduction and Teratology

See **Toxicology, Carcinogenicity Studies, Reproduction and Teratology Studies** and **Mutagenicity Studies** for discussion on animal data.

Dependence Liability

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

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

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 not significantly different from placebo. Administration of a dose of 20 mg of intravenous *d*-amphetamine produced significant positive subjective responses on these scales.

Psychiatric

Pre-existing Psychosis

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

Screening Patients for Bipolar Disorder

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

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children/adolescents with ADHD without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be

appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

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

Suicidal Behavior and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behavior. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behavior, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behavior should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Neurologic

Seizures
There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Tics
Amphetamines have been reported to exacerbate motor and phonic tics in Tourette's syndrome. Therefore, careful clinical evaluation for tics in Tourette's syndrome in patients and their families should precede use of stimulant medications.

Ophthalmologic

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment (see **Contraindications**).

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon
Stimulants, such as 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.

Special Populations

Pregnant Women
The effects of VYVANSE on labour and delivery in humans are unknown.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took *d*-amphetamine sulfate with lovastatin during the first trimester of pregnancy.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d,l*-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function (see **Toxicology, Reproduction and Teratology Studies**).

Non-teratogenic Effects

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

VYVANSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women
Amphetamines are excreted in human milk. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics

ADHD
Amphetamines are not recommended for use in pediatric patients with ADHD under 6 years of age. Long-term effects of amphetamines in children have not been well established (see **Warnings and Precautions, Suppression of Growth; Toxicology, Effects on Growth**).

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

Renal Impairment
Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73m^2), the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis (see **Dosage and Administration; Action and Clinical Pharmacology, Special Populations and Conditions**).

Lisdexamfetamine and d-amphetamine are not dialyzable.

Effects on Ability to Operate Machinery or Vehicles
Patients should find out how VYVANSE will affect them before engaging in activities such as operating machinery or vehicles, as VYVANSE may impair the ability to engage in these activities.

ADVERSE REACTIONS

Attention Deficit Hyperactivity Disorder (ADHD)

Adverse Drug Reaction Overview
The ADHD pre-marketing development program for VYVANSE included exposures in a total of 992 participants in clinical trials (345 pediatric patients aged 6 to 12 years, 233 adolescent patients aged 13 to 17 years, 358 adult patients and 56 healthy adult subjects). Of these, 345 pediatric patients (aged 6 to 12 years) were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study, 233 adolescent (aged 13 to 17 years) patients were evaluated in one controlled clinical study, and 358 adult patients were evaluated in one controlled clinical study and one open-label extension study.

The safety information for the ADHD indication included in this section is based on data from the 4-week parallel-group controlled clinical trials in children, adolescent and adult patients with ADHD. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

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

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

Adverse drug reactions (ADRs) observed with VYVANSE treatment mainly reflect side effects commonly associated with amphetamine use. In ADHD clinical trials, approximately a third of pediatric, adolescent and adult subjects treated with VYVANSE reported decreased appetite and insomnia. Other very common adverse drug reactions include dry mouth, headache and upper abdominal pain. Stimulant side effects generally occur early in treatment and tend to decrease over time[8].

Adverse Events Associated with Discontinuation of Treatment in ADHD Clinical Trials
Nine percent (20/218) of VYVANSE-treated children aged 6 to 12 years discontinued due to adverse events compared to 1% (1/72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, decreased appetite, insomnia, and rash (2/218 each; 1%).

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

In the controlled adult trial, 6% (21/358) of VYVANSE-treated patients discontinued due to adverse events compared to 2% (1/62) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were 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%).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Adverse reactions reported in the ADHD controlled trials in children (aged 6 to 12 years), adolescents (aged 13 to 17 years) and adult patients treated with VYVANSE (incidence of 1% or greater) and greater than that observed in placebo-treated patients are presented in Table 1 to Table 3.

The children clinical trial was a Phase 3, randomized, multi-center, double-blind, parallel-group, placebo-controlled study in 290 children aged 6 to 12 years with ADHD. Adverse drug reactions

with the highest subject incidence rates (≥5.0%) in VYVANSE treatment groups combined were decreased appetite, insomnia, upper abdominal pain, headache, irritability, weight decreased, vomiting, nausea and dizziness. All of these adverse drug reactions are typical side effects of amphetamine products. 54.1% of these adverse drug reactions occurred within the first week of treatment with VYVANSE, when all of the active-treated subjects received VYVANSE 30 mg.

Three hundred and fourteen (314) adolescent subjects (aged 13 to 17 years) with ADHD were enrolled in a Phase 3, randomized, double-blind, multi-center, placebo-controlled, parallel-group, forced-dose titration, safety and efficacy study of VYVANSE. The most common ADRs (≥5.0%) reported with VYVANSE treatment reflected side effects commonly associated with amphetamine use. These included decreased appetite, headache, insomnia, weight decreased and irritability; there was no apparent dose effect for these events among VYVANSE treatment groups. Most ADRs tended to occur early during the course of treatment and their incidence generally decreased over time despite the forced-dose titration schedule of the study.

Four hundred and twenty (420) adult subjects with ADHD were enrolled in a Phase 3, randomized, double-blind, multi-center, placebo-controlled, parallel-group, forced-dose titration, safety and efficacy study of VYVANSE. The most common ADRs (≥5.0%) reported with VYVANSE treatment reflected side effects commonly associated with amphetamine use. These included decreased appetite, dry mouth, headache, insomnia, nausea, diarrhea, anxiety, anorexia and initial insomnia; there was no apparent dose effect for these events among VYVANSE treatment groups. Most ADRs tended to occur early during the course of treatment and their incidence generally decreased over time despite the forced-dose titration schedule of the study.

Small increases in heart rate were observed with VYVANSE use. These changes were small in magnitude and are known effects of amphetamine use. No significant differences were observed among the treatment groups in systolic blood pressure and diastolic blood pressure.

Table 1 Adverse Drug Reactions Reported by 1% or More of Child Patients with ADHD (Aged 6 to 12 Years) Taking VYVANSE in a 4-Week Clinical Trial			
Body System	Preferred Term	VYVANSE (n=218)	Placebo (n=72)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Vomiting	9%	4%
	Nausea	6%	3%
	Dry Mouth	5%	0%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
Investigations	Weight Decreased	9%	1%
Metabolism and Nutrition Disorders	Decreased Appetite	39%	4%
	Anorexia	2%	0%
Nervous System Disorders	Headache	12%	10%
	Dizziness	5%	0%
	Somnolence	2%	1%
	Psychomotor Hyperactivity	1%	0%
Psychiatric Disorders	Insomnia	19%	3%
	Irritability	10%	0%
	Initial Insomnia	4%	0%
	Affect Lability	3%	0%
	Tic	2%	0%
	Aggression	1%	0%
	Agitation	1%	0%
	Obsessive-Compulsive Symptoms	1%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

Note: This table includes those events for which the incidence in patients taking VYVANSE was greater than the incidence in patients taking placebo. ADRs for which the incidence was greater or equal in patients taking placebo: Fatigue.

Uncommon adverse drug reactions (reported by ≥0.1% to <1% of pediatric patients with ADHD taking VYVANSE) in a 4-week clinical trial include:

Cardiac Disorders: Palpitation, tachycardia
Eye Disorders: Mydriasis, vision blurred
Gastrointestinal Disorders: Diarrhea
General Disorders and Administration Site Conditions: Feeling jittery
Immune System Disorders: Hypersensitivity
Investigations: Blood pressure increased
Psychiatric Disorders: Depression, dysphoria, logorrhea
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Table 2 Adverse Drug Reactions Reported by 1% or More of Adolescent Patients with ADHD (Aged 13 to 17 Years) Taking VYVANSE in a 4-Week Clinical Trial			
Body System	Preferred Term	VYVANSE (n=233)	Placebo (n=77)
Cardiac Disorders	Palpitations	2%	1%
Gastrointestinal Disorders	Dry Mouth Nausea	4% 4%	1% 3%
General Disorder and Administration Site Conditions	Fatigue	4%	3%
Investigations	Weight Decreased Blood Pressure Increased	9% 1%	0% 0%
Metabolism and Nutrition	Decreased Appetite Anorexia	34% 2%	3% 0%
Nervous System Disorders	Headache Tremor	15% 2%	13% 0%
Psychiatric Disorders	Insomnia Irritability Initial Insomnia Affect Lability	11% 7% 3% 1%	4% 4% 0% 0%
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	1%	0%

Note: This table includes those events for which the incidence in patients taking VYVANSE was greater than the incidence in patients taking placebo. ADRs for which the incidence was greater or equal in patients taking placebo: Diarrhea, Dizziness and Vomiting.

Uncommon adverse drug reactions (reported by ≥0.1% to <1% of adolescent patients with ADHD taking VYVANSE) in a 4-week clinical trial include:

Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Abdominal pain upper
General Disorders and Administration Site Conditions: Feeling jittery, pyrexia
Psychiatric Disorders: Aggression, anxiety, dermatillomania, restlessness
Nervous System Disorders: Psychomotor hyperactivity, somnolence
Skin and Subcutaneous Tissue Disorders: Rash, urticaria
Reproductive System and Breast Disorders: Erectile dysfunction

Table 3 Adverse Drug Reactions Reported by 1% or More of Adult Patients with ADHD Taking VYVANSE in a 4-Week Clinical Trial			
Body System	Preferred Term	VYVANSE (n=358)	Placebo (n=62)
Cardiac Disorders	Palpitations	2%	0%
	Tachycardia	1%	0%
Gastrointestinal Disorders	Dry Mouth	26%	3%
	Nausea	7%	0%
	Diarrhea	7%	0%
	Abdominal Pain Upper	3%	2%
General Disorder and Administration Site Conditions	Feeling Jittery	4%	0%
Investigations	Weight Decreased	3%	0%
	Blood Pressure Increased	3%	0%
Metabolism and Nutrition Disorders	Decreased Appetite	27%	2%
	Anorexia	5%	0%
Nervous System Disorders	Headache	21%	13%
	Tremor	2%	0%
Psychiatric Disorders	Insomnia	19%	5%
	Anxiety	6%	0%
	Initial Insomnia	5%	3%
	Middle Insomnia	4%	0%
	Agitation	3%	0%
	Restlessness	3%	0%
	Libido Decreased	1%	0%
	Logorrhea	1%	0%
Reproductive System and Breast Disorders	Erectile Dysfunction	1%	0%
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	2%	0%
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	3%	0%
	Rash	1%	0%

Note: This table includes those events for which the incidence in patients taking VYVANSE was greater than the incidence in patients taking placebo. ADRs for which the incidence was greater or equal in patients taking placebo: Dizziness, Fatigue and Irritability.

Uncommon adverse drug reactions (reported by ≥0.1% to <1% of adult patients with ADHD taking VYVANSE) in a 4-week clinical trial include:

Eye Disorders: Vision blurred
Gastrointestinal Disorders: Vomiting
General Disorders and Administration Site Conditions: Pyrexia
Psychiatric Disorders: Affect lability, depression, dermatillomania, dysphoria, euphoria, tic
Nervous System Disorders: Psychomotor hyperactivity, somnolence
Skin and Subcutaneous Tissue Disorders: Urticaria

Weight Loss and Suppression of Growth in Pediatric Patients with ADHD
In the studies conducted in children and adolescents, VYVANSE demonstrated a dose-dependent effect on subjects' body weight over four weeks (see **Warnings and Precautions, Suppression of Growth**).

Weight Loss in Adults with ADHD
In the 4-week adult trial, the dose-dependent effect of VYVANSE on body weight was similar to the pediatric studies.

Long-Term Extension Studies in ADHD
Three long-term, open-label extension studies were conducted over 12 months in 274 children (aged 6-12 years; 147 subjects completed), 269 adolescents (aged 13-17 years; 156 subjects completed), and 349 adults (aged 18-55 years; 191 subjects completed), respectively. VYVANSE was generally safe and well tolerated in each study with a safety profile consistent with stimulant treatment.

Binge Eating Disorder (BED)

Adverse Events Overview
The clinical development program for VYVANSE in treatment of BED included exposure in a total of 1252 patients with BED, aged 18 to 55, in five clinical trials, including an open-label extension. Of these, 288 BED patients received the drug for at least a year, and 608 patients for at least six months. Patients with cardiovascular risk factors other than obesity and smoking were excluded.

Adverse events were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

The most commonly observed adverse events reported with exposure to VYVANSE in BED across the five studies (> 5%) were: dry mouth, insomnia, headache, decreased appetite, nausea, upper respiratory tract infection, nasopharyngitis, tachycardia, constipation, irritability, anxiety, feeling jittery, fatigue and diarrhea. The commonly occurring TEAEs are generally consistent with the known safety profile of VYVANSE.

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

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

Adverse Events Leading to Discontinuation of Treatment in BED Clinical Trials

The discontinuation rate due to adverse events was 9% in 1252 BED patients. The more common events leading to discontinuation were: blood pressure increased/hypertension (0.8%), insomnia (0.7%), anxiety (0.6%), tachycardia (0.6%) and irritability (0.5%).

Clinical Trial Adverse Events

> *Because clinical trials are conducted under very specific conditions the adverse events rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse event information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Treatment-emergent adverse events reported in VYVANSE-treated patients, with an incidence of 2% or greater and greater than that observed in placebo treated patients, from two 12-week randomized, double-blind, multicenter, parallel-group, placebo-controlled dose-optimization studies in adults aged 18-55 years with moderate to severe BED, are presented in Table 4.

Table 4 Treatment-Emergent Adverse Events Reported by 2% or More of Adult Patients with BED Taking VYVANSE, and at incidence rates greater than for placebo, in 12-Week Clinical Trials			
System Organ Class	Preferred Term	VYVANSE (n=373)	Placebo (n=372)
Cardiac Disorders	Palpitations	3%	2%
Gastrointestinal Disorders	Dry Mouth	36%	7%
	Nausea	9%	6%
	Constipation	6%	1%
	Diarrhea	4%	2%
	Abdominal Pain Upper	2%	0%
	Dyspepsia	2%	1%
	Vomiting	2%	1%
General Disorders and Administration Site Conditions	Irritability	7%	5%
	Feeling Jittery	6%	1%
	Fatigue	6%	5%
	Energy Increased	2%	0%
Infections and Infestations	Urinary Tract Infection	2%	0%
	Gastroenteritis	2%	1%
Investigations	Increased Heart Rate[a]	7%	1%
	Weight Decreased	4%	0%
	Blood Pressure Increased	3%	2%
Metabolism and Nutrition Disorders	Decreased Appetite[b]	8%	2%
Nervous System Disorders	Headache	16%	9%
	Paraesthesia, Hypoaesthesia	3%	1%
	Dysgeusia[c]	2%	1%
Psychiatric Disorders	Insomnia[d]	20%	7%
	Anxiety	5%	1%
	Nightmare	2%	0%
	Restlessness	2%	0%
Reproductive System and Breast Disorders	Erectile dysfunction[e]	2%	0%
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	4%	0%
	Pruritis	2%	1%

[a] Includes the preferred terms Heart Rate Increased and Tachycardia.
[b] Decreased appetite includes preferred terms Anorexia and Decreased appetite.
[c] Dysgeusia includes preferred terms of dysgeusia, ageusia, hypogeusia and hypergeusia
[d] Insomnia includes preferred terms of Insomnia, Initial Insomnia and Middle Insomnia.
[e] Denominator includes only male subjects (VYVANSE n=49, Placebo n=56)

Less Common Clinical Trial Adverse Events

The adverse events listed below are based on evaluation of data from pre-marketing phase 2-3 studies based on a pooled database of a total of 4 placebo-controlled studies (including open-label portion when applicable). In these studies, multiple doses of VYVANSE were administered to 988 patients. All reported events are included except those already listed in Table 4, those too general to be informative, and those not reasonably associated with the use of the drug. In some cases, separate event terms have been consolidated to facilitate meaningful presentation. Events are further classified within System Organ Class categories and enumerated in order of decreasing frequency using the following definitions: common (occurring in less than 10/100 patients, but at least 1/100), uncommon (occurring in less than 1/100, but at least 1/1000 patients) or rare (occurring in less than 1/1000 but at least in 1/10,000 patients).

Ear and Labyrinth Disorders: *Uncommon:* vertigo, tinnitus
Eye Disorders: *Uncommon:* vision blurred
Gastrointestinal Disorders: *Common:* abdominal discomfort, abdominal pain; *Uncommon:* post-tussive vomiting
General Disorders and Administration Site Conditions: *Uncommon:* chest pain, pyrexia
Investigations: *Uncommon:* blood pressure diastolic increased, blood pressure systolic increased
Musculoskeletal and Connective Tissue Disorders: *Uncommon:* myalgia
Nervous System Disorders: *Common:* tremor; *Uncommon:* psychomotor hyperactivity, memory impairment, syncope, dizziness postural, resting tremor
Psychiatric Disorders: *Common:* bruxism, nervousness; *Uncommon:* depressed mood, loggorhea, agitation, affect lability, depression, tachyphrenia, euphoric mood, libido decreased, dermatillomania, depressive symtoms, dysphoria, hypomania, loss of libido, major depression
Respiratory, Thoracic and Mediastinal Disorders: *Uncommon:* dyspnea, dyspnea exertional
Skin and Subcutaneaous Tissue Disorders: *Uncommon:* rash, alopecia, rash pruritic
Vascular Disorders: *Uncommon:* hypertension, diastolic hypertension, Raynaud's Phenomenon

Multiple events may have been reported by a single patient. It is important to emphasize that although the events reported did occur during treatment with VYVANSE, they were not necessarily caused by it.

Post-Market Adverse Drug Reactions

System Organ Class	Preferred Term
Cardiac Disorders	Cardiomyopathy Palpitations
Eye Disorders	Diplopia Mydriasis Vision Blurred
Gastrointestinal Disorders	Constipation
General Disorders and Administration Site Disorders	Chest Pain Fatigue
Hepatobiliary Disorders	Eosinophilic Hepatitis
Immune System Disorders	Anaphylactic Reaction Hypersensitivity
Musculoskeletal and Connective Tissue Disorders	Rhabdomyolysis
Nervous System Disorders	Dysgeusia Dyskinesia Restlessness Seizure Somnolence Tremor
Psychiatric Disorders	Aggression Agitation Anxiety Bruxism Depression Dermatillomania Dysphoria Euphoria Hallucination Logorrhea Mania Psychotic Episodes Suicidal Behavior Tic
Skin and Subcutaneous Tissue Disorders	Angioedema Hyperhidrosis Stevens-Johnson Syndrome Urticaria
Vascular Disorders	Raynaud's Phenomenon

Suicidal Behavior and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see **Warnings and Precautions, Suicidal Behavior and Ideation**).

DRUG INTERACTIONS

Drug-Drug Interactions

Proton Pump Inhibitors
These agents act on proton pumps by blocking acid production thereby reducing gastric acidity. A proton pump inhibitor (omeprazole) had no effect on the pharmacokinetics of VYVANSE (lisdexamfetamine dimesylate).

In Vivo Study on Cytochrome P450 (CYP) Substrates
An in vivo human study of lisdexamfetamine dimesylate (70 mg) in healthy adults did not result in any clinically meaningful effect on the pharmacokinetics of drug substrates metabolized by CYP1A2 (200 mg caffeine), CYP2D6 (30 mg dextromethorphan), CYP2C19 (40 mg omeprazole), or CYP3A (0.025 mg/kg midazolam) (see **Detailed Pharmacology**).

Agents Whose Blood Levels May be Impacted by VYVANSE
Extended-release guanfacine:
In a drug interaction study, administration of an extended-release guanfacine (4 mg) to healthy adult volunteers in combination with VYVANSE (50 mg) induced a 19% increase in guanfacine maximum plasma concentrations; whereas, exposure (area under the curve; AUC) was increased by 7%. These small changes are not expected to be clinically meaningful. In this study, no effect on *d*-amphetamine exposure was observed following co-administration of extended-release guanfacine and VYVANSE. Drug interaction studies have not been conducted with higher doses of lisdexamfetamine dimesylate.

Extended-release venlafaxine:
In a drug interaction study, administration of 225 mg extended-release venlafaxine, a CYP2D6 substrate, in combination with 70 mg VYVANSE induced a 9% decrease in the C_{max} and 17% decrease in the AUC for the primary active metabolite o-desmethylvenlafaxine and a 10% increase in C_{max} and 13% increase in AUC for venlafaxine. These small changes are not expected to be clinically meaningful. In this study, no effect on *d*-amphetamine exposure was observed following co-administration of extended-release venlafaxine and VYVANSE. VYVANSE (*d*-amphetamine) may be a weak inhibitor of CYP2D6. Lisdexamfetamine has no effect on the AUC and C_{max} of the composite of venlafaxine and o-desmethylvenlafaxine.

Agents and Conditions that Alter Urinary pH and Impact the Urinary Excretion and Half-Life of Amphetamines
Ascorbic acid and other agents and conditions that acidify urine increase urinary excretion and decrease the half-life of amphetamines. Sodium bicarbonate and other agents and conditions that alkalinize urine, decrease urinary excretion and extend the half-life of amphetamines.

Monoamine Oxidase Inhibitors
VYVANSE is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors (MAOIs). MAOIs and amphetamines, when co-administered, can increase the release of norepinephrine and other monoamines. This can cause severe headaches

and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results (see **Contraindications**).

Serotonergic Drugs
On rare occasions, serotonin syndrome has occurred in association with the use of amphetamines, such as VYVANSE, when given in conjunction with serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). It has also been reported in association with overdose of amphetamines, including VYVANSE (see **Overdosage**). There were no reported cases of serotonin syndrome when VYVANSE was administered with SSRIs and SNRIs in clinical trials. As this syndrome may result in potentially life-threatening conditions (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma), treatment with serotonergic drugs should be discontinued if such events occur and supportive symptomatic treatment should be initiated. VYVANSE should be used with caution in combination with serotonergic and/or neuroleptic drugs (e.g. triptans, certain tricyclic antidepressants and opiate analgesics, lithium, St. John's Wort, MAOI) due to the risk of serotonergic syndrome (see **Contraindications**).

Agents Whose Effects May be Reduced by Amphetamines
Adrenergic blockers:
As expected by their pharmacologic action, adrenergic blockers are inhibited by amphetamines.

Agents Whose Effects May be Potentiated by Amphetamines
Norepinephrine:
Amphetamines enhance the adrenergic effect of norepinephrine.

Modafinil:
Modafinil with amphetamines may cause increases in blood pressure and heart rate and may result in additive effects; their concomitant use is not recommended.

Agents that May Reduce the Effects of Amphetamines
Chlorpromazine:
Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines.

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

Pimozide:
Pimozide may block the action of amphetamines, and concomitant use of the two medications is not recommended.

Drug-Food Interactions

Capsule Formulation
Food (a high fat meal or yogurt) or orange juice does not affect the observed AUC and C_{max} of *d*-amphetamine 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 hrs at fasted state to 4.7 hrs after a high-fat meal or to 4.8 hours with orange juice). After an 8-hour fast, the AUC for *d*-amphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Chewable Tablet Formulation
Food (a high-fat meal) does not affect the C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of d-amphetamine in healthy adults (N=23) after a single 60 mg dose of VYVANSE chewable tablets. Food delays the mean T_{max} of d-amphetamine by approximately 1 hour (from 3.90 hours at fasted state to 4.89 hours after a high fat meal).

Drug-Laboratory Interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels particularly in the evening, and thus may affect urinary steroid determinations.

DOSAGE AND ADMINISTRATION

Cardiovascular Risks

VYVANSE should not be used in patients with symptomatic cardiovascular disease including coronary artery disease nor in patients with moderate to severe hypertension (see **Contraindications**). Blood pressure and pulse should be monitored in all patients taking VYVANSE (see **Warnings and Precautions, Cardiovascular**).

VYVANSE should generally not be used in patients with known serious structural cardiac abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD or BED drugs (see **Contraindications** and **Warnings and Precautions**).

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD or BED should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other sympathomimetic drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with

relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during sympathomimetic medication treatment for ADHD or BED should undergo a prompt cardiac evaluation.

Periodic Evaluation of CV Status
Patients who are considered to need extended treatment with VYVANSE should undergo periodic evaluation of their cardiovascular status (see **Warnings and Precautions**).

General Dosing Considerations

VYVANSE (lisdexamfetamine dimesylate) capsules or chewable tablets should be taken in the morning. Afternoon doses should be avoided because of the potential for insomnia.

VYVANSE may be taken with or without food.

VYVANSE capsules may be taken whole, or the capsule may be opened and the entire contents emptied and mixed with yogurt or in a glass of water or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder in the yogurt or liquid. The contents should be mixed until completely dispersed. The patient should consume the entire mixture of yogurt or liquid **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. The patient should not take anything less than one capsule per day and a single capsule should not be divided.

VYVANSE chewable tablets must be chewed thoroughly before swallowing. The patient should not take anything less than one chewable tablet per day and a single chewable tablet should not be divided.

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 **Action and Clinical Pharmacology, Pharmacokinetics**).

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

In patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis (see **Warnings and Precautions, Special Populations; Action and Clinical Pharmacology, Special Populations and Conditions).**

Recommended Dose and Dosage Adjustment

Attention Deficit Hyperactivity Disorder (ADHD)

Treatment of ADHD (Children, Adolescents and Adults)

VYVANSE should not be used in patients under 6 years of age.

The usual starting dose is 30 mg once daily in the morning, whether a patient is starting ADHD treatment for the first time or switching from another medication. When in the judgment of the clinician a lower dose is appropriate, a patient may begin treatment with 20 mg once daily in the morning.

If a dose increase is warranted in the judgment of the physician, daily dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals.

The maximum VYVANSE dose should not exceed 60 mg/day. In clinical studies, doses of up to 70 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 30 mg/day, and adverse events and discontinuations were more frequent at higher doses. Doses greater than 70 mg/day of VYVANSE have not been studied.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

The effectiveness of VYVANSE has not been studied in adults over 55 years of age (see **Action and Clinical Pharmacology**).

Long-term Use

Pharmacological treatment of ADHD may be needed for extended periods. The efficacy of VYVANSE in maintaining symptom response in children and adolescent patients (aged 6 to 17 years) with ADHD was studied in a 6-week, placebo-controlled randomized withdrawal trial in subjects following treatment with open-label VYVANSE for at least 26 weeks. The efficacy of VYVANSE in maintaining symptom response in adult patients (aged 18 to 55 years) with ADHD was studied in a 6-week, placebo-controlled randomized withdrawal trial in subjects with documentation of open-label treatment with VYVANSE for a minimum of 6 months. Subjects assigned to VYVANSE in the randomized withdrawal phase continued on the same dose used to confirm response in the open-label phase (see **Clinical Trials**).

The efficacy of VYVANSE in ADHD has been evaluated separately in both children and adolescents for up to four weeks, and in adults for up to ten weeks. In a separate controlled trial of a combined population of children and adolescents, the efficacy of VYVANSE has been evaluated for up to seven weeks.

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

Binge Eating Disorder (BED)

Treatment of Moderate to Severe BED (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.

VYVANSE has not been studied, and is not recommended for use in pediatrics patients (less than 18 years of age) with BED. VYVANSE has not been studied in adults over 55 years of age.

VYVANSE should be prescribed for the shortest duration that is clinically indicated in order to minimize exposure to the CV risk in this population; the risk-benefit profile of the drug for the individual patient should be periodically re-evaluated. (see **Warnings and Precautions, Cardiovascular**).

OVERDOSAGE

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

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggression, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

The prolonged duration of action of VYVANSE should be considered when treating patients with overdose.

Lisdexamfetamine and d-amphetamine are not dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lisdexamfetamine dimesylate is a prodrug of *d*-amphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

Pharmacokinetics

Pharmacokinetic studies of *d*-amphetamine after oral administration of lisdexamfetamine dimesylate have been conducted in healthy adult (capsule and chewable tablet formulations) and pediatric (aged 6 to 12 years) (capsule formulation) patients with ADHD.

Absorption
After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract.

Capsule Formulation
In 18 pediatric patients (aged 6 to 12 years) with ADHD, the T_{max} of *d*-amphetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate 30 mg, 50 mg, or 70 mg after an 8-hour overnight fast. The T_{max} of lisdexamfetamine dimesylate was approximately one hour. Linear pharmacokinetics of *d*-amphetamine after single-dose oral administration of VYVANSE capsules was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years; and in adults over a range of 50 mg to supratherapeutic dose of 150 mg.

Food (a high fat meal or yogurt) or orange juice does not affect the observed AUC and C_{max} of *d*-amphetamine in healthy adults after single-dose oral administration of 70 mg of VYVANSE capsules. Food prolongs T_{max} by approximately one hour (from 3.8 hrs at fasted state to 4.7 hrs after a high-fat meal or to 4.8 hrs with orange juice). After an 8-hour fast, the AUC for *d*-amphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Weight/Dose normalized AUC and C_{max} were 22% and 12% lower, respectively, in adult females than in males on Day 7 following a 70 mg/day dose of lisdexamfetamine for seven days. Weight/Dose normalized AUC and C_{max} values were the same in girls and boys following single doses of 30 mg to 70 mg.

Chewable Tablet Formulation
In healthy adult subjects (N=18), the chewable lisdexamfetamine dimesylate tablet formulation, as evaluated by C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of d-amphetamine has shown comparable bioavailability when compared to the capsule formulation after a single-dose oral administration

under fasting condition. The mean T_{max} (SD) of d-amphetamine was 4.4 (1.18) hours following a single 60 mg dose of lisdexamfetamine dimesylate administered in chewable tablet form after a 10-hour overnight fast. The T_{max} of lisdexamfetamine was approximately 1 hour. The d-amphetamine C_{max} pharmacokinetic parameter following administration of the 60 mg chewable tablet in adults exhibited low inter-subject (20.89% [95% CI: 14.85, 31.57]), intra-subject (8.37% [95% CI: 6.62, 11.37]) and subject by treatment interaction (4.15% [95% CI: 1.39, 7.34]) variability.

Food (a high-fat meal) does not affect C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of d-amphetamine in healthy adults (N=23) after a single-dose of 60 mg of VYVANSE chewable tablets. Food delays the mean T_{max} of d-amphetamine by approximately 1 hour (from 3.90 hrs in fasted state to 4.89 hours after a high fat meal).

Distribution
There is no accumulation of *d*-amphetamine (as measured by AUC) at steady state in healthy adults and no accumulation of lisdexamfetamine dimesylate after once-daily dosing for seven consecutive days.

Metabolism
Lisdexamfetamine dimesylate is hydrolyzed in the blood to *d*-amphetamine, which is responsible for the drug's activity, and L-lysine. Lisdexamfetamine is not metabolized by cytochrome P450 enzymes.

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid.

Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Excretion
Following the oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to six healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by eight hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers.

Special Populations and Conditions

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

In a study of 47 subjects aged 55 years of age or older, amphetamine clearance was approximately 0.7 L/hr/kg for subjects 55-74 years of age and 0.55 L/hr/kg for subjects ≥75 years of age. This is slightly reduced compared to younger adults (approximately 1 L/hr/kg for subjects 18-45 years of age). Reduced amphetamine clearance does not appear to be related to kidney function as measured by creatinine clearance.

Gender
Systemic exposure to *d*-amphetamine is similar for men and women given the same mg/kg dose.

Race
Formal pharmacokinetic studies for race have not been conducted.

Renal Impairment
In a pharmacokinetic study of lisdexamfetamine in subjects with normal and impaired renal function, d-amphetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2) (see **Warnings and Precautions, Special Populations; Dosage and Administration**).

STORAGE AND STABILITY

Capsule Formulation
Dispense in a tight, light-resistant container as defined in the USP.
Store at 15-30°C (59-86°F).

Chewable Tablet Formulation
Store at 15-30°C (59-86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

VYVANSE capsules and chewable tablets are designed for once-a-day oral administration.

VYVANSE capsules / chewable tablets contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg* of lisdexamfetamine dimesylate. Corresponding *d*-amphetamine base equivalence as follows:

Lisdexamfetamine dimesylate	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	70 mg*
d-amphetamine base equivalence	3.0 mg	5.9 mg	8.9 mg	11.9 mg	14.8 mg	17.8 mg	20.8 mg*
* Not applicable to chewable tablets							

VYVANSE capsules contain the following inactive ingredients: croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The capsule shells contain edible ink, gelatin, titanium dioxide (E171), and one or more of the following: FD&C Yellow #6 (E110), FD&C Blue #1 (E133), FD&C Red #3 (E127), FDA/E172 Black Iron Oxide, FDA/E172 Yellow Iron Oxide.

VYVANSE capsules 10 mg: pink body/pink cap (imprinted S489 10 mg), bottles of 100.
VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted S489 20 mg), bottles of 100.
VYVANSE capsules 30 mg: white body/orange cap (imprinted S489 30 mg), bottles of 100.
VYVANSE capsules 40 mg: white body/blue green cap (imprinted S489 40 mg), bottles of 100.
VYVANSE capsules 50 mg: white body/blue cap (imprinted S489 50 mg), bottles of 100.
VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted S489 60 mg), bottles of 100.
VYVANSE capsules 70 mg: blue body/orange cap (imprinted S489 70 mg), bottles of 100.

VYVANSE chewable tablets contain the following inactive ingredients: artificial strawberry flavouring, colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, and sucralose.

VYVANSE chewable tablets 10 mg: white to off-white round shaped tablet debossed with '10' on one side and 'S489' on the other, bottles of 100.
VYVANSE chewable tablets 20 mg: white to off-white hexagonal shaped tablet debossed with '20' on one side and 'S489' on the other, bottles of 100.
VYVANSE chewable tablets 30 mg: white to off-white arc triangular shaped tablet debossed with '30' on one side and 'S489' on the other, bottles of 100.
VYVANSE chewable tablets 40 mg: white to off-white capsule shaped tablet debossed with '40' on one side and 'S489' on the other, bottles of 100.
VYVANSE chewable tablets 50 mg: white to off-white arc square shaped tablet debossed with '50' on one side and 'S489' on the other, bottles of 100.
VYVANSE chewable tablets 60 mg: white to off-white arc diamond shaped tablet debossed with '60' on one side and 'S489' on the other, bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

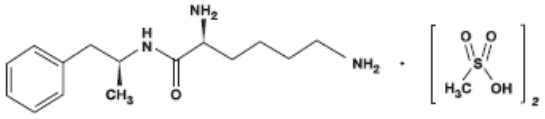
Drug Substance

Proper name: lisdexamfetamine dimesylate

Chemical name:
(2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate

Molecular formula and molecular mass:
$C_{15}H_{25}N_3O \bullet (CH_4O_3S)_2$ 455.60

Structural formula:



Physicochemical properties: White to off-white powder that is highly soluble in water.

CLINICAL TRIALS

Efficacy Studies – Attention Deficit Hyperactivity Disorder (ADHD)

Study Demographics and Trial Design

Table 5 Summary of Patient Demographics for Clinical Trials in ADHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
NRP104.301	Randomized, double-blind, placebo-controlled, parallel-group study conducted in children aged 6 to 12 years who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type).	Patients were randomized to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of VYVANSE or placebo once daily in the morning for four weeks.	n=285	9.0 years (6 to 12)	Male: 69.1% Female: 30.9%
NRP104.201	Double-blind, placebo- and active-controlled, randomized, multi-dose, 3-period and 3-treatment crossover, study of children aged 6 to 12 years who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type) conducted in a laboratory classroom setting.	Following a 3-week open-label dose titration with mixed salts amphetamine extended-release capsules, patients were randomized with respect to treatment sequence for the same dose of mixed salts amphetamine extended-release capsules (10, 20, or 30 mg), VYVANSE (30, 50, or 70 mg), or placebo once daily in the morning for one week each treatment.	n=50	9.1 years (6 to 12)	Male: 62% Female: 38%

Table 5 Summary of Patient Demographics for Clinical Trials in ADHD					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
SPD489-305	Double-blind, randomized, placebo-controlled, parallel-group study conducted in adolescents aged 13 to 17 years who met DSM-IV criteria for ADHD.	In this 4-week study, patients were randomized in a 1:1:1:1 ratio to a daily morning dose of VYVANSE (30, 50 or 70 mg/day) or placebo for a double-blind stepwise forced-dose titration (3 weeks) followed by a 1-week Dose Maintenance Period. All subjects receiving VYVANSE were initiated on 30 mg for the first week of treatment. Subjects assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose.	n=310	14.6 years (13 to 17)	Male: 70.3% Female: 29.7%

Table 5 Summary of Patient Demographics for Clinical Trials in ADHD					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
NRP104.303	Double-blind, randomized, placebo-controlled, parallel-group, forced dose titration study conducted in adults aged 18 to 55 years who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type).	In this 4-week forced-dose titration study, subjects were randomly assigned in a 2:2:2:1 ratio of each of the three active doses vs. placebo to a daily morning dose of VYVANSE or placebo for four weeks. All VYVANSE groups started at 30 mg/day. Subjects randomized to 70 mg titrated to that dose over a 2-week period; those randomized to 50 mg titrated to that dose over a 1-week period; those randomized to 30 mg began dosing on 30 mg/day during Week 1 and remained on that dose throughout the study.	n=420	35.1 years (18 to 55)	Male: 54.3% Female: 45.7%

Study Results (ADHD)

Children with ADHD

Table 6 Results of Study NRP104.301 in ADHD (Children Aged 6 to 12 Years)		
Primary Endpoint	**Associated value and statistical significance for Drug at specific dosages**	**Associated value and statistical significance for Placebo or active control**
ADHD Rating Scale (ADHD-RS) total score change from baseline at treatment endpoint for the ITT population	Significant improvement in patient behavior was observed at endpoint for all active treatment groups. LS Mean (SE)* 30 mg: -21.8 (1.60) 50 mg: -23.4 (1.56) 70 mg: -26.7 (1.54) Comparison (placebo-adjusted difference): LS Mean (95% CI†) -15.58 (-20.78, -10.38) p<0.0001 -17.21 (-22.33, -12.08) p<0.0001 -20.49 (-25.63, -15.36) p<0.0001	LS Mean (SE)* -6.2 (1.56)

* Treatment effect: p<0.0001 (2-way ANCOVA)

† Dunnett's test

CI: Confidence Interval; SE: Standard Error; LS: Least Squares

Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at Week 1 and continued throughout the entire 4-week treatment period for all VYVANSE doses compared to placebo in children aged 6 to 12 years (Table 6). Parents (based on Conner's Parent Rating Scale) reported significant improvement in behavior throughout the day at approximately 10 am, 2 pm, 6 pm in the VYVANSE group when compared to placebo.

Table 7 Results of Study NRP104.201 in ADHD (Children Aged 6 to 12 Years)		
Primary Endpoints	**Associated value and statistical significance for Drug at specific dosages**	**Associated value and statistical significance for Placebo or active control**
Average of SKAMP-deportment scores across the treatment assessment day, using a mixed-effects model of analysis of variance (ANOVA) for the ITT population	LS Mean (SE) 0.8 (0.1)	LS Mean (SE) mixed salts amphetamine extended-release capsules (10 mg, 20 mg, and 30 mg combined): 0.8 (0.1) Placebo: 1.7 (0.1)
	Difference in LS Mean (95% CI) of VYVANSE vs. placebo: -0.9 (-1.1, -0.7)*	Difference in LS Mean (95% CI) of mixed salts amphetamine extended-release capsules vs. placebo: -0.9 (-1.1, -0.7)*
	Difference in LS Mean (95% CI) of VYVANSE vs. mixed salts amphetamine extended-release capsules: -0.1 (-0.3, 0.1)	

* p<0.0001 (2-way ANOVA with treatment and period effects)
CI: Confidence Interval; LS: Least Squares; SE: Standard Error

A significant improvement in patient (aged 6 to 12 years) behavior, based upon the average of investigator ratings on the Swanson, Kotkin, Agler, M.Flynn and Pelham (SKAMP)-deportment scores across the eight sessions of a 12-hour treatment day (assessments conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose), was observed between patients who received VYVANSE compared to patients who received placebo (Table 7).

The results of the secondary efficacy measures (SKAMP-Attention, Clinical Global Impression Improvement [CGI-I], number of math problems attempted [PERMP-A] and number of math problems worked correctly [PERMP-C]) were supportive of the primary efficacy endpoint. On the CGI-I scale, both VYVANSE and mixed salts amphetamine extended-release capsules scores indicated significant improvement compared with placebo. In addition, LS means of Permanent Product Measure of Performance [PERMP] average scores for combined doses of active treatments across the treatment day were highly significant compared with placebo, with both associated with robust increases in the number of attempted and correct math problems.

Analog Classroom Study

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study was conducted in children aged 6 to 12 years (n=129) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose titration with VYVANSE (30, 50, 70 mg), patients were randomly assigned to continue VYVANSE or placebo once daily in the morning for one week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-deportment scores at 1.5 hours post-dose (primary endpoint) and across all seven post-dose sessions of a 13-hour treatment day (assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0,

12.0 and 13.0 hours post-dose), was observed between patients who received VYVANSE compared to patients who received placebo.

Adolescents with ADHD

Table 8 Results of Study SPD489-305 in ADHD (Adolescents Aged 13 to 17 Years)

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
ADHD Rating Scale (ADHD-RS) total score change from baseline at treatment endpoint for the FAS population	Significant improvements in ADHD symptoms were observed at endpoint for all VYVANSE doses compared to placebo. LS Mean (SE)* 30 mg: -18.3 (1.25) 50 mg: -21.1 (1.28) 7 0 mg: -20.7 (1.25) Comparison (placebo-adjusted difference): LS Mean (95% CI†) -5.5 (-9.7, -1.3) p=0.0056 -8.3 (-12.5, -4.1) p<0.0001 -7.9 (-12.1, -3.8) p<0.0001	LS Mean (SE)* -12.8 (1.25)

* Treatment effect: p<0.0001 (2-way ANCOVA)
† Dunnett's test
CI: Confidence Interval; FAS: Full Analysis Set; LS: Least Squares; SE: Standard Error

Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at endpoint for all VYVANSE doses compared to placebo in adolescents aged 13 to 17 years (Table 8). The improvement in the ADHD-RS-IV total score demonstrated in the primary efficacy analysis was supported by the results of the ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscale analyses at endpoint. Consistent with the primary efficacy result, efficacy was demonstrated at endpoint and at every study visit for all three VYVANSE treatment groups. The mean ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscale scores consistently decreased from Visit 1 to Visit 4, and at every visit there was a consistently larger reduction in the subscale scores in VYVANSE treatment groups compared to placebo. At endpoint and at all study visits, the mean change from baseline in the ADHD-RS-IV subscale scores for all three VYVANSE treatment groups was statistically significantly different from placebo, representing an improvement in ADHD symptomatology compared to placebo.

The results of the secondary efficacy measure were supportive of the primary efficacy endpoint. On the CGI-I scale, VYVANSE scores indicated significant improvement compared with placebo.

Children and Adolescents with ADHD

A double-blind, randomized, placebo- and active-controlled parallel-group, dose-optimization study was conducted in children and adolescents aged 6 to 17 years (total 317 subjects [Full Analysis Set population], 229 (72.2%) subjects aged 6 to 12 years and 88 (27.8%) subjects aged 13 to 17 years) who met DSM-IV criteria for ADHD; subjects previously treated with the active control who had not responded were not enrolled into the study. In this eight-week study, patients were randomized to a daily morning dose of VYVANSE (30, 50 or 70 mg/day), active control (included for trial sensitivity) or placebo (1:1:1). The study consisted of 3 periods, as follows: 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 4-week Dose Optimization Period, subjects were titrated until an optimal dose, based on TEAEs and clinical judgment, was reached.

Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed for VYVANSE at endpoint compared to placebo (Table 9). The results of the secondary efficacy measures (CGI-I, change in CHIP-CE: PRF Achievement Domain) were supportive of the primary efficacy endpoint and statistically significantly different from placebo.

Table 9 Results of Study SPD489-325 in ADHD (Children and Adolescents Aged 6 to 17 Years)

Primary Endpoints	**Associated value and statistical significance for Drug at specific dosages**	**Associated value and statistical significance for Placebo or active control**
ADHD Rating Scale (ADHD-RS) total score change from baseline at treatment endpoint for the FAS population	Significant improvements in ADHD symptoms were observed at endpoint compared to placebo. LS Mean (SE)* -24.3 (1.16) Comparison (placebo-adjusted difference): LS Mean (95% CI) -18.6 (-21.5, -15.7) p<0.001	LS Mean (SE)* -5.7 (1.13)

* Treatment effect: p<0.001 (2-way ANCOVA)
CI: Confidence Interval; FAS: Full Analysis Set; LS: Least Squares; SE: Standard Error

Randomized Withdrawal Study (6 weeks double-blind randomized withdrawal in subjects following treatment with open-label VYVANSE for at least 26 weeks)

A double-blind, placebo-controlled, randomized withdrawal study was conducted in children and adolescents aged 6 to 17 years who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in the preceding study SPD489-325 and 40 subjects directly enrolled. A total of 262 subjects were in the open-label Full Analysis Set population, 185 (70.6%) subjects aged 6 to 12 years and 77 (29.4%) subjects aged 13 to 17 years. In order to ensure that the appropriate population was included in the randomized withdrawal period to evaluate the long-term maintenance of efficacy, subjects were treated with open-label VYVANSE for an extended period (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. ADHD-RS Total Score is a measure of core symptoms of ADHD. Of patients that maintained open-label treatment response, 157 were 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. Maintenance of efficacy was demonstrated based on the significantly lower proportion of treatment failure among VYVANSE subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period (see Figure 1). 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. For the majority of subjects (70.3%) who were treatment failures, ADHD symptoms worsened at or before the Week 2 visit following randomization.

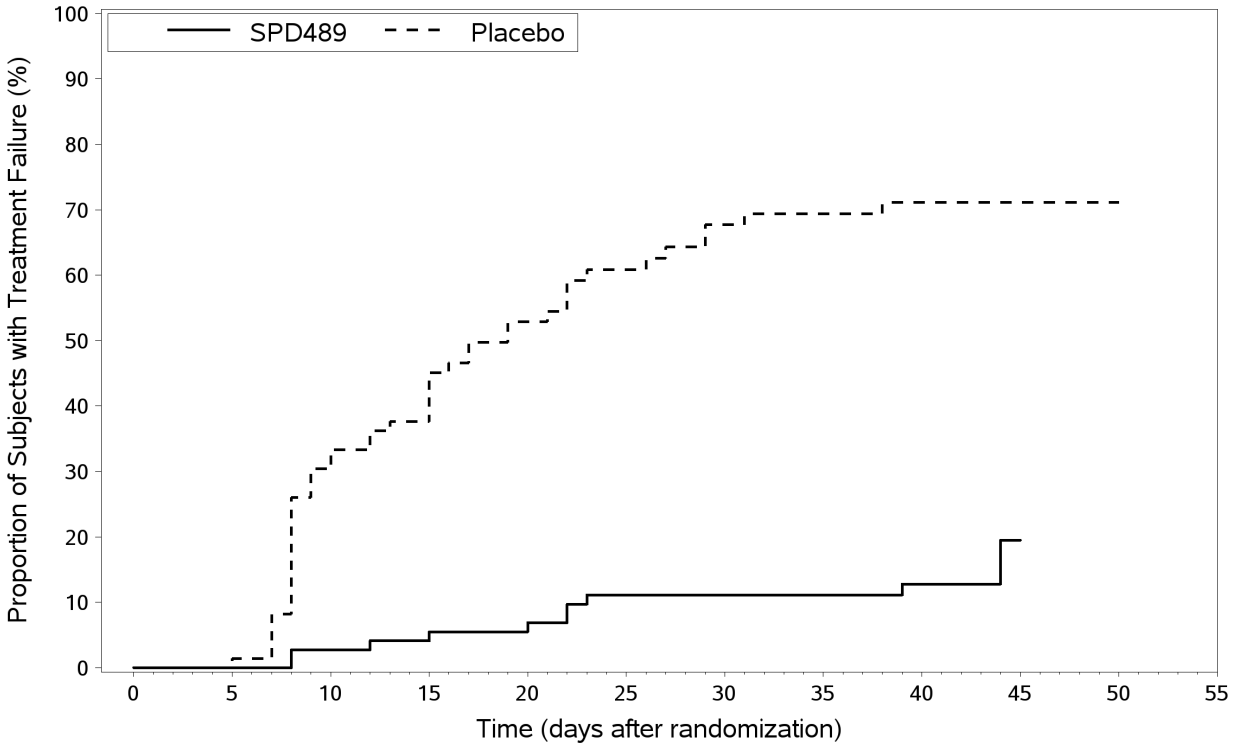


Figure 1 Kaplan-Meier Estimation of Proportion of Patients with Treatment Failure (children and adolescents)

Adults with ADHD

Table 10 Results of Study NRP104.303 in ADHD (Adults Aged 18 to 55 Years)		
Primary Endpoints	**Associated value and statistical significance for Drug at specific dosages**	**Associated value and statistical significance for Placebo or active control**
ADHD Rating Scale (ADHD-RS) total score change from baseline at treatment endpoint for the ITT population	Significant improvement in ADHD symptoms was observed at endpoint for all VYVANSE doses. LS Mean (SE)* 30 mg: -16.2 (1.06) 50 mg: -17.4 (1.05) 70 mg: -18.6 (1.03) Comparison (placebo-adjusted difference): LS Mean (95% CI†) -8.04 (-12.14, -3.95) p<0.0001 -9.16 (-13.25, -5.08) p<0.0001 -10.41 (-14.49, -6.33) p<0.0001	LS Mean (SE)* -8.2 (1.43)

* Treatment effect: p<0.0001 (2-way ANCOVA)
† Dunnett's test
CI: Confidence Interval; LS: Least Squares; SE: Standard Error

Significant improvements in ADHD symptoms, based upon investigator ratings on the ADHD Rating Scale (ADHD-RS), were observed at Week 1 and were seen throughout the entire 4-week treatment period for all VYVANSE doses compared to placebo in adults aged 18 to 55 years (Table 10).

The results of the secondary efficacy measure were supportive of the primary efficacy endpoint. On the CGI-I scale, VYVANSE scores indicated significant improvement compared with placebo.

Adult Workplace Environment Study

A second double-blind, placebo-controlled, randomized, crossover design, multi-centered, adult workplace environment (AWE) study, a modified analog classroom study of VYVANSE to simulate a workplace environment, was conducted in adults (n=142) who met DSM-IV-TR criteria for ADHD. Following a 4-week open-label dose optimization with VYVANSE (30, 50, 70 mg), patients were randomly assigned to continue VYVANSE or placebo once daily in the morning for one week each treatment. Significant improvements in patient performance, based upon the Permanent Product Measure of Performance (PERMP) scores, a skill-adjusted math test that measures attention in ADHD, were demonstrated at all post-dose time points measured between patients who received VYVANSE compared to patients who received placebo. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose.

At the optimized dose strength, significant improvements based upon the PERMP-A (number of math problems attempted) score and PERMP-C (number of math problems answered correctly) scores were demonstrated at all post-dose time points measured between patients who received VYVANSE compared to patients who received placebo. Secondary measures of Adult ADHD-RS with prompts total score, hyperactivity/impulsivity subscale score, and the inattentiveness subscale score were also supportive of the primary efficacy endpoint and statistically significantly different from placebo. On the CGI-I scale, a significantly larger percentage of subjects receiving VYVANSE were improved compared to placebo during the crossover visits.

Randomized Withdrawal Study (6 weeks double-blind randomized withdrawal in subjects with documentation of open-label treatment with VYVANSE for a minimum of 6 months)

A double-blind, placebo-controlled, randomized withdrawal design study was conducted in adults aged 18 to 55 years (n=123) who met DSM-IV criteria for ADHD. At study entry, subjects must have had documentation of treatment with VYVANSE for a minimum of 6 months and had to demonstrate treatment response as defined by CGI-S ≤3 and Total Score on the ADHD-RS with adult prompts <22. ADHD-RS Total Score is a measure of core symptoms of ADHD. Subjects that maintained treatment response at Week 3 of the open-label treatment phase (n=116) were eligible to enter the double-blind randomized withdrawal phase (6 weeks duration), and received their entry dose of VYVANSE (n=56) or placebo (n=60). The efficacy for subjects maintaining treatment with VYVANSE was demonstrated by the significantly lower proportion of treatment failure (<9%) compared to subjects receiving placebo (75%) in the double-blind randomized withdrawal phase (see Figure 2). Treatment failure was defined as a ≥50% increase in the ADHD-RS with adult prompts Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase.

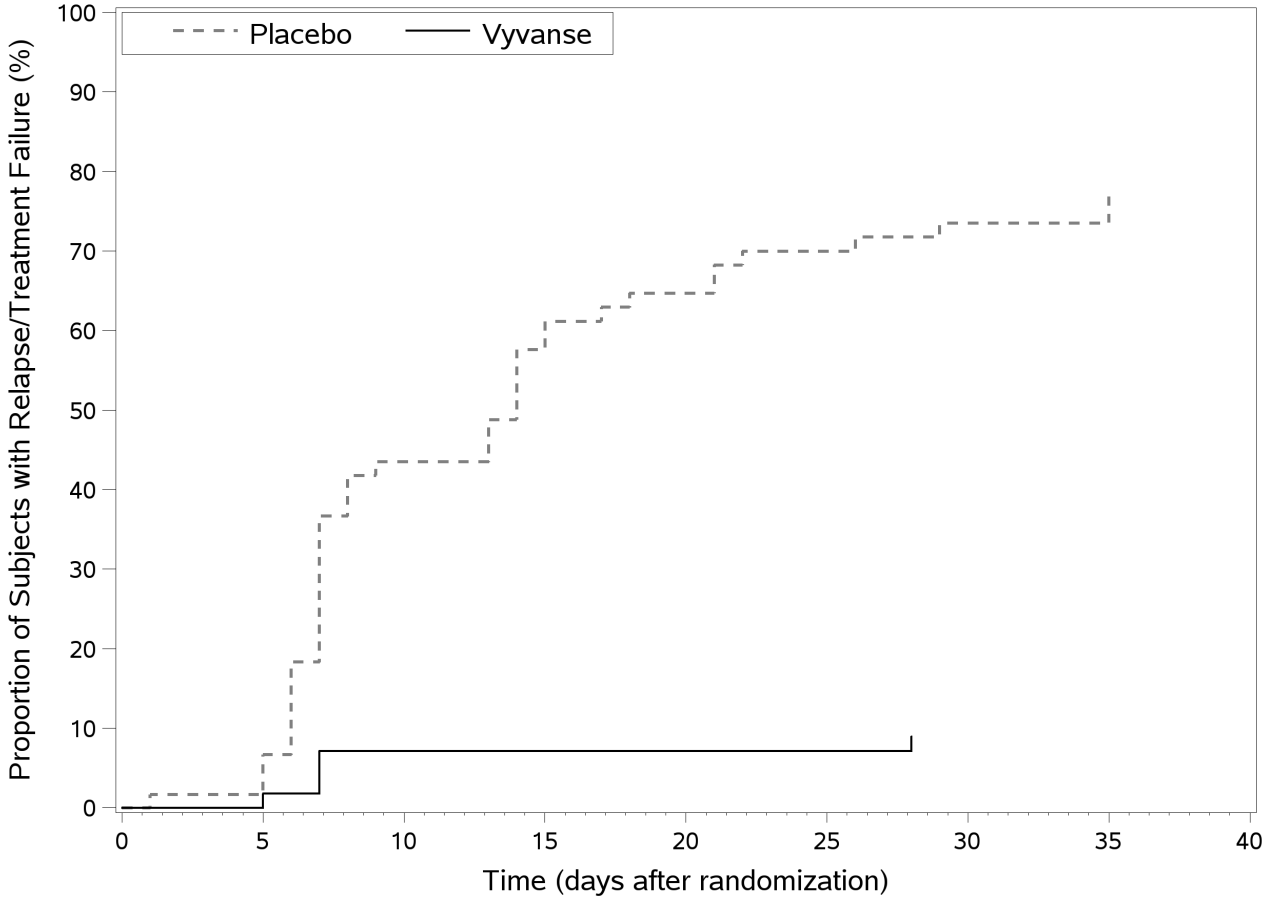


Figure 2 Kaplan-Meier Estimation of Proportion of Patients with Treatment Failure (adults)

Executive Function (Self-regulation) Behaviors Study in ADHD

A 10-week, double-blind, placebo-controlled study was conducted to evaluate change in executive function behaviors, key quality of life outcomes, and ADHD symptoms in adults with ADHD. The study enrolled adults aged 18 to 55 years (n=161) who met DSM-IV criteria for ADHD and had a total score of ≥65 on Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) Global Executive Composite (GEC) T-score by subject-report and a score of ≥28 using the Adult ADHD-RS with prompts at the Baseline visit. The difference in LS mean change from baseline to week 10 for subject-reported BRIEF-A GEC T-score (-11.2) was significantly better in the VYVANSE group compared with placebo ($p<0.0001$). Secondary efficacy measures of Adult ADHD Impact Module (AIM-A), ADHD-RS with adult prompts, CGI and the ADHD Index T-score of the Conners' Adult ADHD Rating Scale – Observer: Short Version (CAARS-O:S) were all significantly better in the VYVANSE group compared with placebo.

Binge Eating Disorder (BED)

Study Results (BED)

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 in adults aged 18-55 years with moderate to severe BED (Study SPD489-343: N=374, Study SPD489-344: N=350). A diagnosis of BED was confirmed using DSM-IV criteria for BED. Requirement of moderate to severe BED was based on having at least 3 binge days per week (as assessed for 2 weeks prior to the baseline visit) and a Clinical Global Impression Severity [CGI-S] score ≥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 and confirmed by the clinician.

Exclusion criteria related to CV safety included moderate or severe hypertension, diabetes, and cardiovascular diseases, such that obesity and smoking were permissible CV risk factors. Comorbid Axis I or Axis II psychiatric disorders that were either controlled with prohibited medications or were uncontrolled and associated with significant symptoms were excluded. Psychotherapy (e.g., supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) or weight loss support (e.g., Weight Watchers) for BED that began ≥3 months prior to the screening visit was allowed, but initiation or change during the study was prohibited; 9 patients (6 on placebo, and 3 on drug) were receiving psychotherapy for BED at the time of informed consent. The majority of patients were women (87%), White (75%), and recruited in sites in the USA (around 90%).

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 50 mg/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 LS mean change from baseline at Week 11/12 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.

Based upon per-protocol MMRM analysis, subjects from both studies on VYVANSE had a statistically significantly greater reduction from baseline compared to placebo in mean number of binge days per week at Weeks 11/12.

Table 11 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[a] (95% CI)
SPD489-343	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)	--
SPD489-344	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.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

In addition, subjects on VYVANSE showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subject rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction on obsessive/compulsive binge eating symptoms as measured by the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score in both studies.

Randomized Withdrawal Study

A double-blind, placebo-controlled, randomized withdrawal design study was conducted to evaluate maintenance of efficacy based on time to relapse between VYVANSE and placebo in adults aged 18 to 55 years (n=267) with moderate to severe BED (DSM-IV-TR diagnosis), who at baseline reported 3 or more binge eating days per week during each of the 2 weeks prior to baseline, and had a CGI-S score of 4 or more.

Exclusion criteria and use of psychotherapy or weight loss support in this study were as described above for the pivotal studies. Two patients were receiving psychotherapy for BED at the time of informed consent. The majority of patients were women (87%), White (84%), and recruited in sites in the USA (around 80%).

The 12-week open-label treatment phase consisted of 4 weeks of dose-optimization and 8 weeks of dose-maintenance. Subjects began treatment at the titration dose of 30 mg/day for 1 week of treatment, and were subsequently titrated to 50 mg/day for the second week. Additional increases to 70 mg/day were made as tolerated and clinically indicated. If, at the end of the third week of dose optimization, the 70 mg dose level was not tolerated, the subject could have been down-titrated to 50 mg; no further dose adjustments were permitted after this time. During the randomised-withdrawal phase, patients received VYVANSE (n=137) or placebo (n=138), at the same optimised dose level as at the end of the open-label phase (50 or 70 mg/day), for up to 26 weeks.

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.

VYVANSE was superior over placebo as measured by time to relapse, the primary efficacy outcome. At the end of the randomized-withdrawal phase, the group continuing on VYVANSE had a lower proportion of relapse (5/136, 3.7%) as compared to the placebo group (42/131, 32.1%). The proportion of patients who completed the randomized withdrawal phase of the study (that is, neither relapsed nor discontinued for other reasons) was 74.5% (102/137) on VYVANSE compared to 36.2% (50/138) on placebo.

Drug Abuse and Dependence Studies

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

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 not significantly different from placebo. Administration of a dose of 20 mg of intravenous *d*-amphetamine produced significant positive subjective responses on these scales.

Comparative Bioavailability Study:

There have been no clinical efficacy studies using VYVANSE chewable tablets. However, in a randomized, open-label, 2-sequence, 4-period replicated crossover study, the bioavailability of d-amphetamine (the primary active lisdexamfetamine metabolite) was compared after a single 60 mg dose administration of VYVANSE chewable tablet versus VYVANSE capsule. The products were administered to healthy adult male and female subjects under fasting conditions. The results from the 18 subjects who completed all four periods of the study are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

d-amphetamine (1 x 60 mg lisdexamfetamine dimesylate) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	VYVANSE Chewable Tablet	VYVANSE Capsule	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{T(0\text{-}96h)}$ (ng·h/mL)	1047.5 1079 (24.0)	1052.9 1087 (24.0)	99.5	95.7 - 103.4
AUC_I (ng·h/mL)	1135.5 1168 (23.1)	1126.2 1161 (23.4)	100.8	97.4 - 104.4
C_{max} (ng/mL)	55.5 56.9 (25.8)	55.9 56.7 (17.8)	99.2	96.1 - 102.4
T_{max}[§] (h)	4.00 (2.0 - 8.0)	4.00 (2.0 - 6.0)		
$T_{½}$[€] (h)	12.7 (18.5)	12.3 (19.4)		

[§] Expressed as the median (range).
[€] Expressed as the arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Binding assays showed that lisdexamfetamine dimesylate lacked affinity for human recombinant DAT and NET transporter sites. Lisdexamfetamine dimesylate was also tested against 62 specific receptor and enzyme sites that could potentially mediate adverse side effects. Lisdexamfetamine dimesylate did not bind significantly to any of these sites.

In pharmacodynamic studies, the effects of orally administered lisdexamfetamine dimesylate were generally comparable to *d*-amphetamine. These studies demonstrated that the total extent of the pharmacological effect of lisdexamfetamine dimesylate (increased locomotor activity) over time was increased while the onset of effect was delayed, compared with an equivalent dose of amphetamine sulphate. This delayed onset is consistent with gradual hydrolysis of lisdexamfetamine dimesylate to release *d*-amphetamine. Parenteral (IV or IN) administration of lisdexamfetamine dimesylate resulted in minimal pharmacological effect as compared to that induced by an equivalent *d*-amphetamine sulphate dose.

In Vitro and Animal Pharmacokinetics

Oral administration of lisdexamfetamine dimesylate in comparison to *d*-amphetamine sulfate demonstrated that the bioavailability (AUC) of *d*-amphetamine from the prodrug was approximately equivalent near therapeutic human equivalent doses (HEDs). At high doses well above the therapeutic range, however, both AUC and C_{max} of *d*-amphetamine from lisdexamfetamine dimesylate were substantially decreased in comparison to AUC and C_{max} of *d*-amphetamine from *d*-amphetamine sulfate.

Absorption of lisdexamfetamine dimesylate orally administered increased non-linearly with increasing dose. The clearance of lisdexamfetamine dimesylate was greater than that of *d*-amphetamine following oral administration. When lisdexamfetamine dimesylate is administered via parenteral routes, there is delayed and gradual release of *d*-amphetamine with substantially attenuated peak concentrations when compared to immediate-release *d*-amphetamine.

Oral administration of lisdexamfetamine dimesylate demonstrated that lisdexamfetamine dimesylate was not detected in rat brain tissue. The major metabolites of lisdexamfetamine dimesylate following oral administration were glucuronidated amphetamine and amphetamine. These two moieties comprised >90% of the total metabolites in plasma after oral dosing.

Following intravenous administration, small amounts of hydroxylated lisdexamfetamine dimesylate were observed in plasma. As in the case of oral administration, the major metabolites from intravenous administration of lisdexamfetamine dimesylate were similar, glucuronidated amphetamine and amphetamine.

In vitro experiments demonstrated that incubation of lisdexamfetamine dimesylate in human hepatic microsomal suspensions resulted in no significant inhibition of a panel of CYP450 isoforms that included CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, nor induction of CYP1A2, CYP2B6 or CYP3A4/5 in cultured fresh human hepatocytes. Lisdexamfetamine dimesylate was stable in the presence of human microsomes and fresh human and rat hepatocytes. No metabolites of lisdexamfetamine dimesylate were observed.

In vitro experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, CYP2D6, and CYP3A4 by one or more metabolites. Although the clinical significance of this interaction is likely to be minimal, consideration should be given when medications metabolised by these pathways are administered.

Lisdexamfetamine dimesylate and *d*-amphetamine are not in vitro substrates for P-gp nor in vitro inhibitors of P-gp transport in monolayers and therefore are unlikely to be involved in clinical interactions with drugs transported by the P-gp pump.

Urinary excretion was the predominant route of elimination accounting for approximately 77% and 87% of the administered dose in males and females, respectively. Excretion in feces accounted for only 10.9% and 3.9% in males and females, respectively. Elimination of radioactivity in urine and feces occurred largely in the first 48 hours post-dose.

Excretion of radioactive labeled lisdexamfetamine dimesylate was evaluated in intact and bile duct cannulated rats. Lisdexamfetamine dimesylate was rapidly eliminated following oral or intravenous administration. Cumulative biliary excretion for the first 48 hours post-dose accounted for approximately 14% and 12% of the dose in male and female rats, respectively. The majority of radioactivity excreted in bile occurred within 8 hours post-dose. The $AUC_{(last)}$ for prodrug was similar for intact and bile duct cannulated rats with no gender differences. On the basis of these findings, bile excretion does not play a major role in lisdexamfetamine dimesylate elimination.

TOXICOLOGY

Acute Toxicity Studies

The LD_{50} value for lisdexamfetamine diHCl in rats was >1000 mg/kg. Lisdexamfetamine diHCl has a 39.9% inherent *d*-amphetamine content. On the basis of this value, the LD_{50} value would be equivalent to either >399 mg/kg of *d*-amphetamine or >548 mg/kg *d*-amphetamine sulfate. Therefore, lisdexamfetamine diHCl is approximately 5-fold less lethal by the oral route than *d*-amphetamine sulfate (LD_{50} value of 96.8 mg/kg).

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.

Subacute and Subchronic Toxicity Studies

In the pivotal 28-day repeat dose rat study, animals were administered lisdexamfetamine dimesylate 20, 40 or 80 mg/kg/day or *d*-amphetamine sulfate at 16 mg/kg/day. There was no mortality, no effects on hematological parameters, and only isolated changes associated with clinical chemistry values for mid- and high-dose group animals. The effects noted at the mid-dosage of lisdexamfetamine dimesylate were similar to those of an equimolar dose of *d*-amphetamine sulfate. No histological findings were present at any dosage of lisdexamfetamine dimesylate.

In the 6-month repeat dose rat study with a 4-week recovery period, animals were administered lisdexamfetamine dimesylate (20 and 40 mg/kg/day) or *d*-amphetamine sulfate (8 and 16 mg/kg/day). No treatment-related pathological changes were apparent, including evaluation of Ki-67 immunolabeling for potential proliferative changes in the liver. Overall there were no toxicologically significant differences between the two test articles.

In the pivotal 28-day repeat dose dog study, animals were administered lisdexamfetamine dimesylate 3, 6 and 12 mg/kg/day or *d*-amphetamine sulfate at 2.4 mg/kg/day. There was no mortality, and no effects on clinical pathology, ophthalmology, ECG, gross necropsy, and histopathology were observed. Other reported effects associated with lisdexamfetamine dimesylate administration were consistent with the known pharmacological effects of *d*-amphetamine. The mid-dose of lisdexamfetamine dimesylate demonstrated pharmacological effects similar to those of an equimolar dose of *d*-amphetamine sulfate.

Juvenile toxicity studies were performed in the rat (4, 10 and 40 mg/kg/day lisdexamfetamine dimesylate) and dog (2, 5 and 12 mg/kg/day). No adverse effects were observed upon nervous system development or reproductive function in the rat or on neurotoxicity or male reproductive endpoints in the dog.

Carcinogenicity Studies

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 two 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.

Reproduction and Teratology Studies

Lisdexamfetamine dimesylate had no apparent effect on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses up to 40 and 120 mg/kg/day, respectively. These doses are approximately 3.2 and 19.2 times (child) and 6.5 and 38.9 times (adult) respectively the maximum recommended dose of 60 mg/day for the treatment of ADHD and 5.6 and 33.4 times (adults) respectively the maximum recommended human daily dose of 70 mg for the treatment of BED, on a mg/m^2 body surface area basis. 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.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d,l*-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

Mutagenicity Studies

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.

Non-Clinical Abuse Data

Non-clinical abuse studies indicate that lisdexamfetamine produced behavioural and subjective effects in rats and monkeys that are qualitatively similar to those of the CNS stimulant *d*-amphetamine, but that are delayed in onset. The rewarding effects, as determined in self-administration studies, are lower than those of methylphenidate or cocaine, but are greater than those of modafinil or placebo.

Effects on Growth

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine from Day 7 to Day 63 of age. These doses are approximately 0.3, 0.8, and 3.2 times the maximum recommended human daily dose of 60 mg for the treatment of ADHD, on a mg/m^2 basis. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four-week drug-free recovery period bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on Day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine for six 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, 1.3, and 3.2 times the maximum recommended human daily dose of 60 mg on a mg/m^2 basis). This effect partially or fully reversed during a 4-week drug-free recovery period.

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PART III: CONSUMER INFORMATION

VYVANSE®*
lisdexamfetamine dimesylate capsules
lisdexamfetamine dimesylate chewable tablets

This leaflet is Part III of a three-part "Product Monograph" published when VYVANSE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VYVANSE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
VYVANSE is a central nervous system stimulant prescription medicine to be used only as follows:

- for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). VYVANSE may be a part of the patient's overall treatment for ADHD. The doctor may also recommend that you/your child have counseling or other therapy.
- to treat moderate to severe Binge Eating Disorder (BED) in adults.

Binge Eating Disorder: Use of other stimulant drugs for weight loss has been associated with serious heart-related problems. It is not known if VYVANSE is safe and effective for weight loss.

What it does:
Attention Deficit Hyperactivity Disorder (ADHD):
Lisdexamfetamine dimesylate, the medicinal ingredient in VYVANSE, helps increase attention (including the ability to follow directions and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD.

Binge Eating Disorder (BED):
Lisdexamfetamine dimesylate, the medicinal ingredient in VYVANSE, may help reduce the number of binge eating days in adults with BED.

When it should not be used:
VYVANSE should not be taken if one or more of the following applies to you/your child:

- allergies to amphetamines or any of the other ingredients in VYVANSE or its container
- sensitive to, allergic to or had a reaction to other stimulant medicines
- advanced arteriosclerosis (hardened arteries)
- symptomatic heart disease
- moderate to severe high blood pressure
- agitated states
- glaucoma, an eye disease
- hyperthyroidism (an overactive thyroid gland)
- are taking or have taken medications from the group called monoamine oxidase inhibitors (MAOI) within the last 14 days
- have a history of drug abuse
- are breastfeeding or plan to breastfeed. VYVANSE passes into breast milk.

VYVANSE has not been studied in, and should not be used in, children with ADHD less than 6 years old.

VYVANSE has not been studied and should not be used in children with BED (younger than 18 years of age).

What the medicinal ingredient is:
Lisdexamfetamine dimesylate

What the nonmedicinal ingredients are:
VYVANSE capsules: Croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The capsule shells contain edible ink, gelatin, titanium dioxide (E171), and one or more of the following: FD&C Yellow #6 (E133), FD&C Blue #1 (E110), FD&C Red #3 (E127), FDA/E172 Black Iron Oxide, FDA/E172 Yellow Iron Oxide.

VYVANSE chewable tablets: artificial strawberry flavouring, colloidal silicon dioxide,croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, and sucralose.

What dosage forms it comes in:
Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg
Chewable Tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg and 60 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
VYVANSE has a potential for abuse, misuse and dependence. (see also Drug Abuse and Dependence below)

The following have been reported with use of medicines such as VYVANSE:

1. Heart-related problems:

- **Sudden death in patients who have heart problems or heart defects**
- **Stroke and heart attack in adults**
- **Increased blood pressure and heart rate**

Sudden death has been reported with drugs used for ADHD treatment in children/adolescents with structural heart abnormalities or other serious heart problems. Although some serious heart problems alone can carry an increased risk of sudden death, VYVANSE generally should not be used in children, adolescents or adults with known structural heart abnormalities, disease of the heart muscle, serious heart rhythm abnormalities or other serious heart disease or conditions.

Binge Eating Disorder: There may be additional heart-related risks in overweight and obese patients.

Tell your doctor if you or your child has any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor may wish to check you or your child carefully for heart problems before starting VYVANSE. Your doctor may wish to check you or your child's blood pressure and heart rate regularly during treatment with VYVANSE.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking VYVANSE.

2. Mental (Psychiatric) problems:

- **New or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, completed suicide)**
- **New or worse bipolar illness, characterized by extreme mood swings, with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness)**
- **New or worse aggressive behavior or hostility**
- **New psychosis (such as hearing voices, believing things that are not true, are suspicious) or new mania (unusually excited, over-active or un-inhibited)**.

These new or worse mental problems may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your doctor about any mental problems you or your child have, or about any personal or family history of suicide, bipolar illness, or depression.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time *during* treatment, particularly at the start or during dose changes, and also *after stopping* VYVANSE. **Should this happen to you, or to those in your care if you are a caregiver or guardian, talk to your doctor immediately. Close observation by a doctor is necessary in this situation.**

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

VYVANSE may not be right for you/your child. Before you/your child use VYVANSE, talk to your doctor or pharmacist if one or more of the following applies to you/your child:

- heart disease or condition, structural heart abnormalities or high blood pressure
- family history of sudden death or death related to heart problems
- participate in strenuous exercise or activities
- take other drugs for ADHD
- have mental problems, or family history of mental problems, including psychosis, mania, bipolar illness, depression or suicide
- have motor tics (hard to control, repeat twitching of any parts of the body) or verbal tics (hard to control repeating of sounds or words) or Tourette's syndrome
- have relatives with motor tics, verbal tics, or Tourette's syndrome
- have a history of seizures (convulsions, epilepsy) or have had an abnormal brain wave test (EEG)
- are pregnant or plan to become pregnant. Taking VYVANSE during pregnancy can cause harm to your baby. If VYVANSE is required during pregnancy, the risk to the unborn baby should be weighed against the benefits for the mother. Your doctor can discuss these issues with you
- have kidney-related problems as your doctor may reduce the dose
- have circulation problems in fingers and toes, including numbness; feeling cold or pain. (This is also known as Raynaud's).

Tell your doctor if you/your child develop any of the above conditions or symptoms while taking VYVANSE.

Drug Abuse and Dependence
Amphetamines have the potential for abuse and misuse. Abuse of amphetamines can lead to dependence and possibly serious heart problems and death. Substance abuse may be less likely in patients with ADHD if they are treated with medication. VYVANSE should only be given under close medical supervision to patients whose condition has been properly diagnosed (see Serious Warnings and Precautions above).

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

Growth in Children
VYVANSE in children may cause slower growth (slowed weight gain and/or height). The doctor will be carefully watching your/your child's height and weight. VYVANSE treatment may be stopped if you/your child are not growing or gaining weight as the doctor expects.

Dangerous activities
Before you/your child perform tasks which may require special attention, such as riding a bike, driving, operating machinery or doing other dangerous activities, wait until you know how you/your child respond to VYVANSE.

INTERACTIONS WITH THIS MEDICATION

It is important to tell your doctor or pharmacist about all medicines that you/your child are taking, including other medicines that a doctor has prescribed, medicines or vitamins that you buy yourself without a prescription, and any herbal remedies. While on VYVANSE, do not take/give your child a new medicine or herbal remedy before checking with you/your child's doctor.

Know the medicines that you/your child take. Keep a list of your/your child's medicines with you to show the doctor and pharmacist.

Drugs that may interact with VYVANSE include:

- Extended-release guanfacine, another medicine for ADHD
- Extended-release venlafaxine, a medicine used to treat depression and anxiety
- Medicines and conditions that make urine more acidic (e.g., ascorbic acid (vitamin C), ammonium chloride, sodium acid phosphate)
- Medicines and conditions that make urine more alkaline (e.g., sodium bicarbonate, acetazolamide, thiazides)
- Medicines to treat depression including monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs)
- Anti-psychotic medicines chlorpromazine, haloperidol and pimozide
- Modafinil
- Medicines used to reduce or increase blood pressure.

PROPER USE OF THIS MEDICATION

Capsules may be swallowed whole with water. Capsules may be opened and the entire contents mixed with yogurt or in a glass of water or orange juice; any compacted powder should be completely broken apart with a spoon. Consume entire yogurt or drink all water or orange juice **immediately**; do not store for future use. A film of inactive ingredients may remain in the glass or container after the mixture is consumed. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and you/your child should not take anything less than one capsule per day.

Chewable tablets must be chewed thoroughly before swallowing. The entire tablet should be taken, and you/your child should not take anything less than one chewable tablet per day.

In order to receive the most benefit from VYVANSE, it is important that VYVANSE be taken only as directed by your/your child's doctor. The doctor may adjust the amount of drug taken until it is right for you/your child. If you/your child have kidney-related problems, your doctor may reduce the dose. From time to time, the doctor may interrupt treatment to check your/your child's symptoms while you/your child are not taking the drug.

Your doctor may do regular checks of the heart and blood pressure while taking VYVANSE. Children should have their height and weight checked often while taking VYVANSE. VYVANSE treatment may be stopped if a problem is found during these check-ups.

As with all medicines, never share VYVANSE with anyone else and administer only the number of VYVANSE capsules or VYVANSE chewable tablets prescribed by your/your child's doctor.

Attention Deficit Hyperactivity Disorder (ADHD) (Adults and Children 6 years of age and older):
Usual dose: 20 mg to 60 mg once a day in the morning, with or without food.
Follow your doctor's instructions on how to take your dose.

Binge Eating Disorder (BED) (Adults):
Starting Dose: 30 mg once a day in the morning with or without food.
Usual Dose: 50 mg to 70 mg once a day in the morning with or without food.
Follow your doctor's instructions on how to take your dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you/your child forget to take your/his or her dose in the morning, wait until the next day and take or have him or her take the usual dose at the usual time in the morning. Do not double dose.

Afternoon doses should be avoided because of the long-acting nature of the drug, including the potential for insomnia.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

When used in ADHD, the most common side effects may include:

- Anorexia, decreased appetite, nausea, vomiting, upper belly pain, diarrhea, dizziness
- Dry mouth
- Headache
- Irritability
- Trouble sleeping
- Weight loss.

When used in BED, the most common side effects may include:

- Constipation, decreased appetite, diarrhea, nausea
- Dry mouth
- Trouble sleeping
- Feeling jittery/restless/racing thoughts
- Headache
- Irritability

- Increased heart rate
- Fatigue
- Anxiety
- Common cold, upper respiratory infection
- Excessive sweating

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Uneven heartbeat (palpitations) (see Warnings and Precautions)**		√	
	Slowing of growth (height and weight) in children		√	
	Anxiety	√		
	New tics		√	
Uncommon	**Allergic Reaction:** Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Trouble with Vision: Eyesight changes or blurred vision		√	
	New Psychotic or Manic Symptoms: -Paranoia, delusions -Hallucinations: seeing, feeling or hearing things that are not real -Mania: feeling unusually excited, over-active, or un-inhibited **(see Warnings and Precautions)**		√	
	Aggressive Behavior or Hostility		√	
	Depression: Feeling sad, loss of interest in usual activities, hopelessness, insomnia, or sleeping too much		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Unknown	**Fits (seizures)**			√
	Liver Disorder (eosinophilic hepatitis): Allergic liver injury seen as possible yellowing of the eyes and/or skin, dark urine, abdominal pain, nausea, vomiting, loss of appetite			√
	Suicidal Behavior: Thoughts or actions about hurting or killing yourself. **(see Warnings and Precautions)**			√
	Serious Skin Condition (Stevens-Johnson Syndrome): Swelling of the skin (angioedema) or serious skin rash seen as severe blisters of the skin and mucous membranes			√
	Cardiomyopathy: Breathlessness or swelling of the legs (signs of heart muscle disease) **(see Warnings and Precautions)**		√	
	Raynaud's Phenomenon: discoloration of the fingers and toes, pain, sensations of cold and/or numbness		√	

This is not a complete list of side effects. For any unexpected effects while taking VYVANSE, contact your doctor or pharmacist.

HOW TO STORE IT

Keep this medication out of the sight and reach of children.

Store VYVANSE Capsules at 15 to 30°C. Protect from light.
Store VYVANSE Chewable Tablets at 15 to 30°C.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about VYVANSE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website www.shirecanada.com , or by calling 1-800-268-2772.

This leaflet was prepared by Shire Pharma Canada ULC
22 Adelaide St. West, Suite 3800
Toronto, Ontario M5H 4E3

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