HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADDERALL XR® safely and effectively. See full prescribing information for ADDERALL XR.

ADDERALL XR (mixed salts of a single-entity amphetamine product) extended-release capsules, for oral use, CII
Initial U.S. Approval: 2001

WARNING: ABUSE, MISUSE, and ADDICTION

See full prescribing information for complete boxed warning.

ADDERALL XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Warnings and Precautions (5.5)	09/2025

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

ADDERALL XR, a CNS stimulant, is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older. (1)

Limitations of Use

The use of ADDERALL XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage. (5.5, 8.4)

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

- Pediatric patients (ages 6 to 17): 10 mg once daily in the morning. Maximum dose for children 6 to 12 years of age is 30 mg once daily. (2.2, 2.3, 2.4)
- Adults: 20 mg once daily in the morning. (2.5)
- Pediatric patients (ages 6 to 17) with severe renal impairment: 5 mg once daily in the morning. Maximum dose for children 6 to 12 years of age with severe renal impairment is 20 mg once daily. (2.6, 8.6)
- Adults with severe renal impairment: 15 mg once daily in the morning. (2.6, 8.6)
- Patients with end stage renal disease (ESRD): Not recommended. (2.6, 8.6)

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

Extended-release capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity or idiosyncrasy to amphetamine. (4)
- During or within 14 days following the administration of monoamine oxidase inhibitors (MAOI). (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease. (5.2)
- Increased Blood Pressure and Heart Rate: Monitor blood pressure and pulse at appropriate intervals. (5.3)
- Psychiatric Adverse Reactions: Prior to initiating ADDERALL XR, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing ADDERALL XR. (5.4)
- Long-Term Suppression of Growth in Pediatric Patients: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.5)
- Seizures: May lower the convulsive threshold. Discontinue in the presence of seizures. (5.6)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Careful observation for digital changes is necessary during ADDERALL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.7)
- Serotonin Syndrome: Increased risk when coadministered with serotonergic agents (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans), but also during overdosage situations. If it occurs, discontinue ADDERALL XR and initiate supportive treatment. (4, 5.8, 10)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating ADDERALL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.9)

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

- Pediatric patients ages 6 to 12: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. (6.1)
- Pediatric patients ages 13 to 17: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness. (6.1)
- Adults: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Alkalinizing agents (GI antacids and urinary): These agents increase blood levels of amphetamine. (2.7, 7.1)
- Acidifying agents (GI and urinary): These agents reduce blood levels of amphetamine. (7.1)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, and ADDICTION

ADDERALL XR® has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout ADDERALL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

1.1 Attention Deficit Hyperactivity Disorder

ADDERALL XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older.

Limitations of Use

The use of ADDERALL XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.5), Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with ADDERALL XR, assess:

- for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating ADDERALL XR *[see Warnings and Precautions (5.9)]*.

2.2 General Administration Information

Individualize the dosage according to the therapeutic needs and response of the patient. Administer ADDERALL XR at the lowest effective dosage.

Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL, (for example, twice daily), may be switched to ADDERALL XR at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

ADDERALL XR extended-release capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

ADDERALL XR may be taken orally with or without food.

ADDERALL XR should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

2.3 Recommended Dosage in Pediatric Patients 6 to 12 Years

In pediatric patients 6 to 12 years of age with ADHD and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children 6 to 12 years of age is 30 mg/day; doses greater than 30 mg/day have not been studied in children. ADDERALL XR has not been studied in children under 6 years of age.

2.4 Recommended Dosage in Pediatric Patients 13 to 17 Years

The recommended starting dose for pediatric patients 13 to 17 years of age with ADHD and are either starting treatment for the first time or switching from another medication is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

2.5 Recommended Dosage in Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

2.6 Dosage in Patients with Renal Impairment

In adult patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2), the recommended dose is 15 mg once daily in the morning. In pediatric patients (6 to 17 years of age) with severe renal impairment, the recommended dose is 5 mg once daily. The maximum dose for children 6 to 12 years of age with severe renal impairment is 20 mg once daily. ADDERALL XR is not recommended in patients with end stage renal disease (ESRD) (GFR <15 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.7 Dosage Modification due to Drug Interactions

Agents that alter urinary pH can impact excretion and alter blood levels of amphetamines. Acidifying agents (e.g., ascorbic acid) decrease blood levels; adjust ADDERALL XR dosage based on clinical response *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

ADDERALL XR 5 mg extended-release capsules: Clear/blue (imprinted ADDERALL XR 5 mg)

ADDERALL XR 10 mg extended-release capsules: Blue/blue (imprinted ADDERALL XR 10 mg)

ADDERALL XR 15 mg extended-release capsules: Blue/white (imprinted ADDERALL XR 15 mg)

ADDERALL XR 20 mg extended-release capsules: Orange/orange (imprinted ADDERALL XR 20 mg)

ADDERALL XR 25 mg extended-release capsules: Orange/white (imprinted ADDERALL XR 25 mg)

ADDERALL XR 30 mg extended-release capsules: Natural/orange (imprinted ADDERALL XR 30 mg)

4 CONTRAINDICATIONS

ADDERALL XR administration is contraindicated in patients:

- known to be hypersensitive to amphetamine, or other components of ADDERALL XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products *[see Adverse Reactions (6.2)]*.
- taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Warnings and Precautions (5.8), Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

ADDERALL XR has a high potential for abuse and misuse. The use of ADDERALL XR exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. ADDERALL XR can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2)]*. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing ADDERALL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store ADDERALL XR in a safe place, preferably locked, and instruct patients to not give ADDERALL XR to anyone else. Throughout ADDERALL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage. Avoid ADDERALL XR use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm).

Monitor all ADDERALL XR-treated patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disease

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating ADDERALL XR treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

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

5.5 Long-Term Suppression of Growth in Pediatric Patients

ADDERALL XR is not approved for use and is not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)].*

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in ADDERALL XR-treated pediatric patients treated with CNS stimulants.

In a controlled trial of ADDERALL XR in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and

20 mg ADDERALL XR. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Chronic use of amphetamines can be expected to cause a similar suppression of growth *[see Adverse Reactions (6.1)]*.

Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

5.6 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 the 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, ADDERALL XR should be discontinued.

5.7 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including ADDERALL XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports and at the therapeutic dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during ADDERALL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for ADDERALL XR-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.8 Serotonin Syndrome

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

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

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

5.9 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including amphetamine, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating ADDERALL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor ADDERALL XR-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.5)]*
- Seizures *[see Warnings and Precautions (5.6)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The premarketing development program for ADDERALL XR included exposures in a total of 1,315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

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

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

Adverse Reactions Leading to Discontinuation of Treatment

In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR-treated patients discontinued due to adverse reactions (including three patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo.

The most frequent adverse reactions leading to discontinuation of ADDERALL XR in controlled and uncontrolled, multiple-dose clinical trials of children (N=595) were anorexia (loss of appetite) (2.9%),

insomnia (1.5%), weight loss (1.2%), emotional lability (1%), and depression (0.7%). Over half of these patients were exposed to ADDERALL XR for 12 months or more.

In a separate placebo-controlled 4 week study in adolescents with ADHD, five patients (2.1%) discontinued treatment due to adverse events among ADDERALL XR-treated patients (N=233) compared to none who received placebo (N=54). The most frequent adverse event leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of ADDERALL XR-treated patients and at a rate at least twice that of placebo) was insomnia (1.3%, n=3).

In one placebo-controlled 4 week study among adults with ADHD with doses 20 to 60 mg, 23 patients (12.0%) discontinued treatment due to adverse events among ADDERALL XR-treated patients (N=191) compared to one patient (1.6%) who received placebo (N=64). The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of ADDERALL XR-treated patients and at a rate at least twice that of placebo) were insomnia (5.2%, n=10), anxiety (2.1%, n=4), nervousness (1.6%, n=3), dry mouth (1.6%, n=3), anorexia (1.6%, n=3), tachycardia (1.6%, n=3), headache (1.6%, n=3), and asthenia (1.0%, n=2).

Adverse Reactions Occurring in Controlled Trials

Adverse reactions reported in a 3 week clinical trial of children and a 4 week clinical trial in adolescents and adults, respectively, treated with ADDERALL XR or placebo are presented in the tables below.

Table 1: Adverse Reactions Reported by 2% or More of Children (6 to 12 Years Old) Receiving ADDERALL XR with Higher Incidence than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Fever	5%	2%
	Infection	4%	2%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Vomiting	7%	4%
	Nausea	5%	3%
	Dyspepsia	2%	1%
Nervous System	Insomnia	17%	2%
	Emotional Lability	9%	2%
	Nervousness	6%	2%
	Dizziness	2%	0%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2: Adverse Reactions Reported by 5% or More of Adolescents (13 to 17 Years Old) Weighing ≤75 kg/165 lbs Receiving ADDERALL XR with Higher Incidence than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite[b]	36%	2%
Nervous System	Insomnia[b] Nervousness	12% 6%	4% 6%[a]
Metabolic/Nutritional	Weight Loss[b]	9%	0%

Note: The following reactions did not meet the criterion for inclusion in *Table 2* but were reported by 2 to 4% of adolescent patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

* Included doses up to 40 mg.

[a] Appears the same due to rounding.

[b] Dose-related adverse reactions.

Table 3: Adverse Reactions Reported by 5% or More of Adults Receiving ADDERALL XR with Higher Incidence than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR (n=191)	Placebo (n=64)
General	Headache Asthenia	26% 6%	13% 5%
Digestive System	Dry Mouth Loss of Appetite Nausea Diarrhea	35% 33% 8% 6%	5% 3% 3% 0%
Nervous System	Insomnia Agitation Anxiety Dizziness Nervousness	27% 8% 8% 7% 13%	13% 5% 5% 0% 13%[a]
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	10%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following reactions did not meet the criterion for inclusion in *Table 3* but were reported by 2 to 4% of adult patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder (e.g., teeth clenching, tooth infection), emotional lability, libido decreased, somnolence, speech disorder (e.g., stuttering, excessive speech), palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

* Included doses up to 60 mg.

[a] Appears the same due to rounding.

Hypertension

In a controlled 4 week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR-treated patients. Similar results were observed at higher doses *[see Warnings and Precautions (5.2)].*

In a single-dose pharmacokinetic study in 23 adolescents with ADHD, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender, and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 and 20 mg ADDERALL XR, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours postdose and not associated with symptoms.

6.2 Adverse Reactions Associated with the Use of Amphetamine, ADDERALL XR, or ADDERALL

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

Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Cardiovascular: Palpitations. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, motor and verbal tics, aggression, anger, logorrhea, dermatillomania, paresthesia (including formication), and bruxism.

Endocrine: Impotence, changes in libido, frequent or prolonged erections.

Eye Disorders: Vision blurred, mydriasis.

Gastrointestinal: Unpleasant taste, constipation, intestinal ischemia, and other gastrointestinal disturbances.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Skin: Alopecia.

Vascular Disorders: Raynaud's phenomenon.

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with Amphetamines

Table 4: Drugs Having Clinically Important Interactions with Amphetamines

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
Intervention	Do not administer ADDERALL XR concomitantly or within 14 days after discontinuing MAOI *[see Contraindications (4)]*.

Serotonergic Drugs	
Clinical Impact	The concomitant use of ADDERALL XR and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during ADDERALL XR initiation or dosage increase. If serotonin syndrome occurs, discontinue ADDERALL XR and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.8)]*.
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of ADDERALL XR and CYP2D6 inhibitors may increase the exposure of ADDERALL XR compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during ADDERALL XR initiation and after a dosage increase. If serotonin syndrome occurs, discontinue ADDERALL XR and the CYP2D6 inhibitor *[see Warnings and Precautions (5.8), Overdosage (10)]*.
Alkalinizing Agents	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Coadministration of ADDERALL XR and gastrointestinal or urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.
Proton Pump Inhibitors	
Clinical Impact	Time to maximum concentration (T_{max}) of amphetamine is decreased compared to when administered alone.
Intervention	Monitor patients for changes in clinical effect and adjust therapy based on clinical response.

7.2 Interference with Laboratory Tests

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

Allow for an adequate washout period between administration of ADDERALL XR and radioactive diagnostic agents used for dopamine transporter (DAT) visualization. ADDERALL XR can interfere with the test results of a radioactive diagnostic agent (ioflupane I-123) that is used for DAT visualization by binding and internalization of the DAT, which may result in lower DAT in the striatum. This may lead to false-positive diagnostic results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Available data from published epidemiologic studies and postmarketing reports on use of prescription amphetamine in pregnant women have not identified a drug-associated risk of major birth defects and miscarriage *(see Data)*. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers taking amphetamines during pregnancy *(see Clinical Considerations)*.

No apparent effects on morphological development were observed in embryo-fetal development studies, with oral administration of amphetamine to rats and rabbits during organogenesis at doses 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. However, in a pre- and postnatal development study, amphetamine (d- to l- ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *(see Data)*.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as ADDERALL XR, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions, increasing the risk of premature delivery. Infants born to mothers taking amphetamines during pregnancy have an increased risk of premature delivery and low birth weight.

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

Data

Animal Data

Amphetamine (d- to l- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD given to adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A study was conducted in which pregnant rats received daily oral doses of amphetamine (d- to l- enantiomer ratio of 3:1) of 2, 6, and 10 mg/kg from gestation Day 6 to lactation Day 20. These doses

are approximately 0.8, 2, and 4 times the MRHD of 20 mg/day given to adolescents, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on Day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of ADDERALL XR have not been established in pediatric patients less than 6 years of age.

The safety and effectiveness of ADDERALL XR have been established in pediatric patients with ADHD 6 years of age and older.

In studies evaluating extended-release amphetamine products, patients 4 to <6 years of age had higher systemic amphetamine exposures than those observed in older pediatric patients at the same dosage. Pediatric patients 4 to <6 years of age also had a higher incidence of adverse reactions, including weight loss.

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including ADDERALL XR, and pediatric patients aged 6 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5)]*.

Juvenile Animal Toxicity Data

Juvenile rats treated with mixed amphetamine salts early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 6 times the maximum recommended human dose (MRHD) given to children on a mg/m^2 basis. No recovery was seen following a drug-free period. A delay in sexual maturation was observed at a dose approximately 6 times the MRHD given to children on a mg/m^2 basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1) of 2, 6, or 20 mg/kg on Days 7 to 13 of age; from Day 14 to approximately Day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.6, 2, and 6 times the MRHD of 30 mg/day, given to children on a mg/m^2 basis. Postdosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was

decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

8.5 Geriatric Use
ADDERALL XR has not been studied in the geriatric population.

8.6 Renal Impairment
Due to reduced clearance of amphetamines in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m^2), the recommended dose should be reduced. ADDERALL XR is not recommended in patients with ESRD (GFR <15 mL/min/1.73 m^2) *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

D-amphetamine is not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
ADDERALL XR contains amphetamine, a Schedule II controlled substance.

9.2 Abuse
ADDERALL XR has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. ADDERALL XR can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of amphetamine may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including ADDERALL XR, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

9.3 Dependence
Physical Dependence

ADDERALL XR may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including ADDERALL XR include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance
ADDERALL XR may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

Clinical Effects of Overdose
Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

Overdose Management
Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of ADDERALL XR should be considered when treating patients with overdose. D-amphetamine is not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

ADDERALL XR extended-release capsules contain mixed salts of a single-entity amphetamine, a CNS stimulant. ADDERALL XR contains equal amounts (by weight) of four salts: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate and amphetamine (D, L)-aspartate monohydrate. This results in a 3.1:1 mixture of dextro- to levo-amphetamine base equivalent.

The 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg strength extended-release capsules are for oral administration. ADDERALL XR contains two types of drug-containing beads (immediate-release and delayed-release) which prolong the release of amphetamine compared to the ADDERALL (immediate-release) tablet formulation.

Each capsule contains:

Capsule Strength	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine (D,L)-Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg
d-amphetamine base equivalence	2.4 mg	4.7 mg	7.1 mg	9.5 mg	11.9 mg	14.2 mg
l-amphetamine base equivalence	0.75 mg	1.5 mg	2.3 mg	3.0 mg	3.8 mg	4.5 mg

Inactive Ingredients and Colors
The inactive ingredients in ADDERALL XR extended-release capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

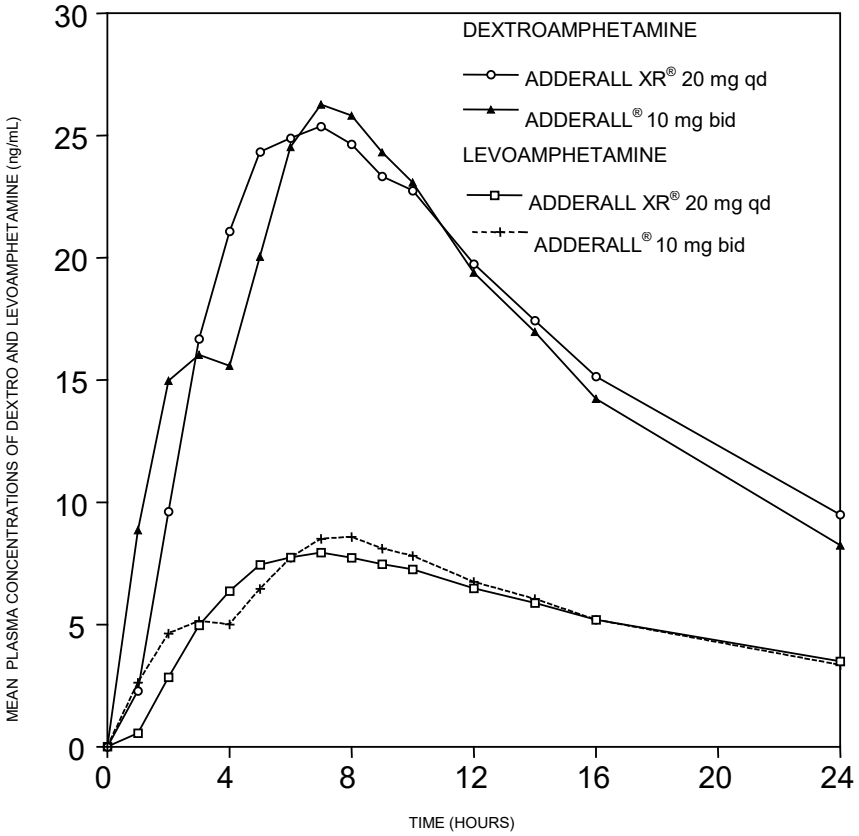
Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR have been conducted in healthy adult and pediatric (children aged 6 to 12 years) subjects, adolescent (13 to 17 years), and children with ADHD. Both ADDERALL (immediate-release) tablets and ADDERALL XR extended-release capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR is about 7 hours, which is about 4 hours longer compared to ADDERALL (immediate-release). This is consistent with the extended-release nature of the product.

Figure 1: Mean d-amphetamine and l-amphetamine Plasma Concentrations Following Administration of ADDERALL XR 20 mg (8 am) and ADDERALL (immediate-release) 10 mg Twice Daily (8 am and 12 noon) in the Fed State.



A single dose of ADDERALL XR 20 mg extended-release capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL (immediate-release) 10 mg twice daily administered 4 hours apart.

The mean elimination half-life for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13 to 17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis, children have a higher clearance than adolescents or adults *(see Special Populations)*.

ADDERALL XR demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents weighing greater than 75 kg/165 lbs, over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hours at fasted state to 7.7 hours after a high-fat meal) for d-amphetamine and 2.7 hours (from 5.6 hours at fasted state to 8.3 hours after a high-fat meal) for l-amphetamine after administration of ADDERALL XR 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR strengths are bioequivalent.

Metabolism and Excretion

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.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30 to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1 to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased *[see Drug Interactions (7)]*.

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR in children (6 to 12 years) and adolescent (13 to 17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_∞) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_Z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20 to 30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8), and Hispanics (N=10).

Patients with Renal Impairment

The effect of renal impairment on d- and l-amphetamine after administration of ADDERALL XR has not been studied. The impact of renal impairment on the disposition of amphetamine is expected to be similar between oral administration of lisdexamfetamine and ADDERALL XR.

In a pharmacokinetic study of lisdexamfetamine in adult subjects with normal and impaired renal function, mean 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). Dialysis did not significantly affect the clearance of d-amphetamine *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which d, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day given to children, on a mg/m^2 basis.

Mutagenesis

Amphetamine, in the enantiomer ratio d- to l- ratio of 3:1, was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility
Amphetamine, in the enantiomer ratio d- to l- 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 (approximately 8 times the maximum recommended human dose of 20 mg/day given to adolescents, on a mg/m^2 basis).

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

14 CLINICAL STUDIES
Pediatric Patients
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6 to 12 (N=584) 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 10 mg, 20 mg, or 30 mg of ADDERALL XR or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg, or 30 mg ADDERALL XR demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

A double-blind, randomized, multicenter, parallel-group, placebo-controlled study was conducted in adolescents aged 13 to 17 (N=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤75 kg/165 lbs) were randomized to fixed-dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg ADDERALL XR or placebo once daily in the morning. Patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75 kg/165 lbs who were randomized to fixed-dose treatment groups receiving final doses of 50 mg and 60 mg ADDERALL XR or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV) total score for the primary cohort. The ADHD-RS-IV is an 18-item scale that measures the core symptoms of ADHD. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adult Patients
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed-dose treatment groups receiving final doses of 20 mg, 40 mg, or 60 mg of ADDERALL XR or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD, were observed at endpoint for all ADDERALL XR doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADDERALL XR 5 mg extended-release capsules: Clear/blue (imprinted ADDERALL XR 5 mg), bottles of 100, NDC 54092-381-01

ADDERALL XR 10 mg extended-release capsules: Blue/blue (imprinted ADDERALL XR 10 mg), bottles of 100, NDC 54092-383-01

ADDERALL XR 15 mg extended-release capsules: Blue/white (imprinted ADDERALL XR 15 mg), bottles of 100, NDC 54092-385-01

ADDERALL XR 20 mg extended-release capsules: Orange/orange (imprinted ADDERALL XR 20 mg), bottles of 100, NDC 54092-387-01

ADDERALL XR 25 mg extended-release capsules: Orange/white (imprinted ADDERALL XR 25 mg), bottles of 100, NDC 54092-389-01

ADDERALL XR 30 mg extended-release capsules: Natural/orange (imprinted ADDERALL XR 30 mg), bottles of 100, NDC 54092-391-01

Dispense in a tight, light-resistant container as defined in the USP.

Store at room temperature, 20 to 25ºC (68 to 77ºF). Excursions permitted to 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of ADDERALL XR, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), Overdosage (10)]*. Advise patients to store ADDERALL XR in a safe place, preferably locked, and instruct patients to not give ADDERALL XR to anyone else.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with ADDERALL XR use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate

Advise patients that ADDERALL XR can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.3)].*

Psychiatric Adverse Reactions

Prior to initiating treatment with ADDERALL XR, adequately screen patients with comorbid depressive symptoms to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and/or depression. Additionally, ADDERALL XR therapy at usual doses may cause treatment-emergent psychotic or manic symptoms in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

Instruct patients beginning treatment with ADDERALL XR about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and in associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or

toes. Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking ADDERALL XR. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with concomitant use of ADDERALL XR and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid) *[see Contraindications (4), Warnings and Precautions (5.8), Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Concomitant Medications

Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions *[see Drug Interactions (7.1)]*. Advise patient or caregiver of steps to take with ADDERALL XR when a laboratory imaging procedure is ordered *[see Drug Interactions (7.2)]*.

Growth

Monitor growth in children during treatment with ADDERALL XR, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5)]*.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's syndrome may occur during treatment with ADDERALL XR. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.9)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADDERALL XR during pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy

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

Lactation

Advise women not to breastfeed if they are taking ADDERALL XR *[see Use in Specific Populations (8.2)]*.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

For more information call 1-877-825-3327.

ADL364

MEDICATION GUIDE
ADDERALL XR® (ADD-ur-all X-R)
(mixed salts of a single-entity amphetamine product)
extended-release capsules, CII

What is the most important information I should know about ADDERALL XR?

ADDERALL XR may cause serious side effects, including:

Abuse, misuse, and addiction. ADDERALL XR has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of ADDERALL XR, other amphetamine containing medicines, and methylphenidate containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of ADDERALL XR or when it is used in ways that are not approved, such as snorting or injection.

- Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with ADDERALL XR and will monitor you or your child during treatment.
- ADDERALL XR may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
- Do not give ADDERALL XR to anyone else. See "**What is ADDERALL XR?**" for more information.
- Keep ADDERALL XR in a safe place and properly dispose of any unused medicine. See "**How should I store ADDERALL XR?**" for more information.

Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

Your healthcare provider should check you or your child carefully for heart problems before starting treatment with ADDERALL XR. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with ADDERALL XR.

- **Increased blood pressure and heart rate.**

  Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with ADDERALL XR.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior or thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

Tell your healthcare provider about any mental problems you or your child have or about a family history of suicide, bipolar illness, or depression.

Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with ADDERALL XR, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is ADDERALL XR?

ADDERALL XR is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years of age and older. ADDERALL XR may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

ADDERALL XR is not recommended for use in children under 6 years of age with ADHD.

ADDERALL XR is a federally controlled substance (CII) because it contains amphetamine that can be a target for people who abuse prescription medicines or street drugs. Keep ADDERALL XR in a safe place to protect it from theft. Never give your ADDERALL XR to anyone else because it may cause death or harm them. Selling or giving away ADDERALL XR may harm others and is against the law.

Who should not take ADDERALL XR?

Do not take ADDERALL XR if you or your child:

- are taking or have stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue
- are allergic to amphetamine products or any of the ingredients in ADDERALL XR. See the end of this Medication Guide for a complete list of ingredients in ADDERALL XR.

Before taking ADDERALL XR tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure, or have a family history of sudden death or heart problems
- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide bipolar illness, or depression
- have kidney problems
- have seizures or have had an abnormal brain wave test (EEG)
- have circulation problems in fingers and toes
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or
- Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if ADDERALL XR will harm the unborn baby. Tell your healthcare provider if you or your child become pregnant or think you may be pregnant during treatment with ADDERALL XR.
    - There is a pregnancy registry for females who are exposed to ADDERALL XR during pregnancy. The purpose of the registry is to collect information about the health of females exposed to ADDERALL XR and their baby. If you or your child becomes pregnant during treatment with ADDERALL XR, talk to your healthcare provider about registering with the National Pregnancy Registry of Psychostimulants at 1-866-961-2388 or visit online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/.
- are breastfeeding or plan to breastfeed. ADDERALL XR passes into breast milk. You or your child should not breastfeed during treatment with ADDERALL XR. Talk to your healthcare provider about the best way to feed the baby during treatment with ADDERALL XR.

Tell your healthcare provider about all of the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ADDERALL XR and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with ADDERALL XR.

Your healthcare provider will decide if ADDERALL XR can be taken with other medicines.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Know the medicines that you or your child take. Keep a list of your or your child's medicines with you to show your healthcare provider and pharmacist when you or your child get a new medicine.

Do not start any new medicine during treatment with ADDERALL XR without talking to your healthcare provider first.

Your healthcare provider may tell you to stop taking ADDERALL XR for a short time before you get certain imaging tests because ADDERALL XR may impact the results of some tests.

How should ADDERALL XR be taken?

- Take ADDERALL XR exactly as prescribed by your or your child's healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take ADDERALL XR 1 time each day in the morning when you first wake up.
- Taking ADDERALL XR in the afternoon may cause trouble sleeping.
- ADDERALL XR can be taken with or without food.
- Swallow ADDERALL XR capsules whole. If you or your child cannot swallow the capsule whole, open it and sprinkle the medicine on applesauce.
  - Swallow all of the applesauce and medicine mixture right away.
  - **Do not** chew the applesauce and medicine mixture.
  - **Do not** store the applesauce sprinkled with ADDERALL XR.
  - **Do not** divide the medicine in the capsule. Take all the contents in the capsule.

If you or your child take too much ADDERALL XR, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of ADDERALL XR?

ADDERALL XR may cause serious side effects, including:

- See **"What is the most important information I should know about ADDERALL XR?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with ADDERALL XR. Your healthcare provider may stop your child's ADDERALL XR treatment if they are not growing or gaining weight as expected.
- **Seizures.** Your healthcare provider may stop treatment with ADDERALL XR if you or your child have a seizure.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon).**
  Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you have or your child have any numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

  Call your healthcare provider right away if you have or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with ADDERALL XR.
- **Serotonin syndrome.** This problem may happen when ADDERALL XR is taken with certain other medicines and may be life-threatening. Stop taking ADDERALL XR and call your healthcare provider or go to the nearest hospital emergency room right away if you or your child develop any of the following signs and symptoms of serotonin syndrome:
  - agitation, hallucinations, coma, or other changes in mental status
  - problems controlling movements or muscle twitching
  - fast heartbeat
  - seizures
  - loss of coordination
  - confusion
  - dizziness
  - change in blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - muscle stiffness or tightness
  - high body temperature (hyperthermia)
- **New or worsening tics or worsening Tourette's Syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with ADDERALL XR.

The most common side effects of ADDERALL XR in children ages 6 to 12 include:

- loss of appetite
- trouble sleeping
- stomach (abdominal) pain
- mood swings
- vomiting
- nervousness
- nausea
- fever

The most common side effects of ADDERALL XR in adolescents ages 13 to 17 include:

- loss of appetite
- trouble sleeping
- stomach (abdominal pain)
- weight loss
- nervousness

The most common side effects of ADDERALL XR in adults include:

- dry mouth
- loss of appetite
- trouble sleeping
- headache
- weight loss
- nausea
- anxiety
- agitation
- dizziness
- fast heartbeat
- diarrhea
- weakness
- urinary tract infections (UTIs)

These are not all the possible side effects of ADDERALL XR.

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

How should I store ADDERALL XR?

- Store ADDERALL XR at room temperature between 68 to 77°F (20 to 25°C).
- Protect ADDERALL XR from light.
- Store ADDERALL XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired ADDERALL XR by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix ADDERALL XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away ADDERALL XR in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep ADDERALL XR and all medicines out of the reach of children.

General information about the safe and effective use of ADDERALL XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADDERALL XR for a condition for which it was not prescribed. Do not give ADDERALL XR to other people, even if they have the same condition. It may harm them and it is against the law.

You can ask your pharmacist or healthcare provider for information about ADDERALL XR that is written for health professionals.

What are the ingredients in ADDERALL XR?

Active ingredient: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate

Inactive ingredients: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide

Distributed by:
Takeda Pharmaceuticals America, Inc, Cambridge, MA 02142

For more information, you may also contact Takeda Pharmaceuticals (the maker of ADDERALL XR) at 1-877-825-3327 or visit the website at http://www.adderallxr.com.

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

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

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

VYVANSE has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including VYVANSE, can result in overdose and death (5.1, 9.2, 10):
- **Before prescribing VYVANSE, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Warnings and Precautions (5.5)	09/2025

----------INDICATIONS AND USAGE----------
VYVANSE is a central nervous system (CNS) stimulant indicated for the treatment of (1):
- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older
- Moderate to severe binge eating disorder (BED) in adults

Limitations of Use:
- The use of VYVANSE is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage (5.5, 8.4)
- VYVANSE is not indicated for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established (5.2)

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

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

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

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)
- Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to amphetamine products or other ingredients in VYVANSE (4)
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- *Risks to Patients with Serious Cardiac Disease:* Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease (5.2)
- *Increased Blood Pressure and Heart Rate:* Monitor blood pressure and pulse. (5.3)
- *Psychiatric Adverse Reactions:* Prior to initiating VYVANSE, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing VYVANSE. (5.4)
- *Long-Term Suppression of Growth in Pediatric Patients:* Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Careful observation for digital changes is necessary during VYVANSE treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue VYVANSE and initiate supportive treatment. (4, 5.7, 10)
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome:* Before initiating VYVANSE, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.8)

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

VYVANSE has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including VYVANSE, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing VYVANSE, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout VYVANSE treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

VYVANSE® is indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older *[see Clinical Studies (14.1)]*.
- Moderate to severe binge eating disorder (BED) in adults *[see Clinical Studies (14.2)]*.

Limitations of Use:

- The use of VYVANSE is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.5), Use in Specific Populations (8.4)]*.
- VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with VYVANSE, assess:

• for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.

• the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating VYVANSE *[see Warnings and Precautions (5.8)]*.

2.2 General Administration Information

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

Information for VYVANSE capsules:

- Swallow VYVANSE capsules whole, or
- Open capsules, empty and mix the entire contents with yogurt, water, or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder. The contents should be mixed until completely dispersed. Consume the entire mixture immediately. It should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass or container once the mixture is consumed.

Information for VYVANSE chewable tablets:

- VYVANSE chewable tablets must be chewed thoroughly before swallowing.

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

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

2.3 Dosage for Treatment of ADHD

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

2.4 Dosage for Treatment of Moderate to Severe BED in Adults

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

2.5 Dosage in Patients with Renal Impairment

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

2.6 Dosage Modifications due to Drug Interactions

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

3 DOSAGE FORMS AND STRENGTHS

*VYVANSE (*lisdexamfetamine dimesylate*) capsules:*

- Capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg)
- Capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg)
- Capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg)
- Capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg)
- Capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg)
- Capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg)
- Capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg)

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

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

4 CONTRAINDICATIONS

VYVANSE is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports *[see Adverse Reactions (6.2)]*.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

VYVANSE has a high potential for abuse and misuse. The use of VYVANSE exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. VYVANSE can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2)]*. Misuse and abuse of CNS stimulants, including VYVANSE, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing VYVANSE, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store VYVANSE in a safe place, preferably locked, and instruct patients to not give VYVANSE to anyone else. Throughout VYVANSE treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage. Avoid VYVANSE use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Some patients may have larger increases.

Monitor all VYVANSE-treated patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

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

Induction of a Manic Episode in Patients with Bipolar Disorder
CNS stimulants may induce a manic or mixed episode. Prior to initiating VYVANSE treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms
CNS stimulants, at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients compared to 0% of placebo-treated patients. If such symptoms occur, consider discontinuing VYVANSE.

5.5 Long-Term Suppression of Growth in Pediatric Patients

VYVANSE is not approved for use and is not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

In a 4-week, placebo-controlled trial of VYVANSE in pediatric patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the VYVANSE groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height *[see Adverse Reactions (6.1)]*.

Closely monitor growth (weight and height) in VYVANSE-treated pediatric patients. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including VYVANSE, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during VYVANSE treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for VYVANSE-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.7 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see Drug Interactions (7.1)]*. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to the active metabolite of VYVANSE (dextroamphetamine). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (7.1)]*.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

Discontinue treatment with VYVANSE and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate VYVANSE with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

5.8 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including amphetamine, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating VYVANSE, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor VYVANSE-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE *[see Contraindications (4)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Attention Deficit Hyperactivity Disorder

The safety data in this section is based on data from the 4-week controlled parallel-group clinical studies of VYVANSE in pediatric and adult patients with ADHD *[see Clinical Studies (14.1)]*.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials
In the controlled trial in pediatric patients ages 6 to 12 years (Study 1), 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)]. Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included abdominal pain upper, dry mouth, weight decreased, dizziness, somnolence, logorrhea, chest pain, anger and hypertension.

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

In the controlled adult trial (Study 7), 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%). Less frequently reported adverse reactions

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

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

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

Adverse Reactions Occurring at an Incidence of 2% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages, 6 to 12 years (Study 1), pediatric patients ages 13 to 17 years (Study 4), and adult patients (Study 7) treated with VYVANSE or placebo are presented in Tables 1, 2 and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

	VYVANSE (n=218)	Placebo (n=72)
Decreased Appetite	39%	4%
Insomnia	22%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%
Anorexia	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

	VYVANSE (n=233)	Placebo (n=77)
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%
Palpitations	2%	1%
Anorexia	2%	0%
Tremor	2%	0%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 7)

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

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

Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD
In a controlled trial of VYVANSE in pediatric patients ages 6 to 12 years (Study 1), mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 1 pound weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in pediatric patients ages 6 to 12 years who received VYVANSE over 12 months suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months were 60.9 and 47.2, respectively). In a 4-week controlled trial of VYVANSE in pediatric patients ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 2.0 pound weight gain for patients receiving placebo.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients ages 7 to 13 years (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in pediatric patients ages 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 pounds and -2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment *[see Warnings and Precautions (5.5)]*.

Weight Loss in Adults with ADHD
In the controlled adult trial (Study 7), mean weight loss after 4 weeks of therapy was 2.8 pounds, 3.1 pounds, and 4.3 pounds, for patients receiving final doses of 30 mg, 50 mg, and 70 mg of VYVANSE, respectively, compared to a mean weight gain of 0.5 pounds for patients receiving placebo.

Binge Eating Disorder

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

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials
In controlled trials of patients ages 18 to 55 years, 5.1% (19/373) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of VYVANSE-treated patients. Less commonly reported adverse reactions (less than 1% or less than twice rate of placebo) included

increased heart rate, headache, abdominal pain upper, dyspnea, rash, insomnia, irritability, feeling jittery and anxiety.

Adverse Reactions Occurring at an Incidence of 5% or More and At Least Twice Placebo Among VYVANSE Treated Patients with BED in Clinical Trials
The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.

Adverse Reactions Occurring at an Incidence of 2% or More and At Least Twice Placebo Among VYVANSE Treated Patients with BED in Clinical Trials
Adverse reactions reported in the pooled controlled trials in adult patients (Study 11 and 12) treated with VYVANSE or placebo are presented in Table 4 below.

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

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, motor and verbal tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, rhabdomyolysis, and intestinal ischemia.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 5 Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer VYVANSE during or within 14 days following the administration of MAOI *[see Contraindications (4)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of VYVANSE and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during VYVANSE initiation or dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.7)]*.
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of VYVANSE and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of VYVANSE compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during VYVANSE initiation and after a dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the CYP2D6 inhibitor *[see Warnings and Precautions (5.7) and Overdosage (10)]*.

Alkalinizing Agents	
Clinical Impact	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of VYVANSE and urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.

7.2 Interference with Laboratory Test

Allow for an adequate washout period between administration of VYVANSE and radioactive diagnostic agents used for dopamine transporter (DAT) visualization. VYVANSE can interfere with the test results of a radioactive diagnostic agent (ioflupane I-123) that is used for DAT visualization by binding and internalization of the DAT, which may result in lower DAT in the striatum. This may lead to false-positive diagnostic results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The limited available data from published literature and postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines *[see Clinical Considerations]*. In animal reproduction studies, lisdexamfetamine dimesylate (a prodrug of d-amphetamine) had no effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis. Pre- and postnatal studies were not conducted with lisdexamfetamine dimesylate. However, amphetamine (d- to l- ratio of 3:1) administration to pregnant rats during gestation and

lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *[see Data]*.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as VYVANSE, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

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

Data

Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 5.5 and 33 times, respectively, the maximum recommended human dose (MRHD) of 70 mg/day given to adults, on a mg/m^2 body surface area basis.

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

ADHD

Safety and effectiveness of VYVANSE have been established in pediatric patients with ADHD ages 6 to 17 years *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

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

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

BED

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

Growth Suppression

Growth should be monitored during treatment with stimulants, including VYVANSE, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

Juvenile Animal Data

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

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m^2 basis for a child. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four-week drug-free recovery period, bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine dimesylate for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m^2 basis for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

8.5 Geriatric Use

Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

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

Lisdexamfetamine and d-amphetamine are not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

9.2 Abuse

VYVANSE has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. VYVANSE can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of lisdexamfetamine, a prodrug of amphetamine, may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including VYVANSE, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Studies of VYVANSE in Drug Abusers

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

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring “Drug Liking”, “Euphoria”, “Amphetamine Effects”, and “Benzedrine Effects” that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

9.3 Dependence

Physical Dependence

VYVANSE may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including VYVANSE include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance
VYVANSE may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

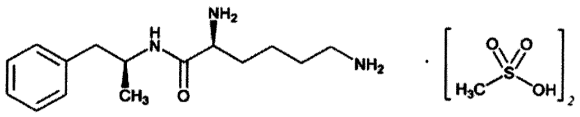
Clinical Effects of Overdose
Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

Overdose Management
Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of VYVANSE should be considered when treating patients with overdose. Lisdexamfetamine and d-amphetamine are not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

VYVANSE (lisdexamfetamine dimesylate), a CNS stimulant, is for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is $C_{15}H_{25}N_3O•(CH_4O_3S)_2$, which corresponds to a molecular weight of 455.60. The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL).

Information for VYVANSE capsules:

VYVANSE capsules contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine).

Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide.

Information for VYVANSE chewable tablets:

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD and BED is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

12.3 Pharmacokinetics

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

Absorption

Capsule formulation
Following single-dose oral administration of VYVANSE capsule (30 mg, 50 mg, or 70 mg) in patients ages 6 to 12 years with ADHD under fasted conditions, T_{max} of lisdexamfetamine and dextroamphetamine was reached at approximately 1 hour and 3.5 hours post dose, respectively.

Weight/Dose normalized AUC and C_{max} values were the same in pediatric patients ages 6 to 12 years as the adults following single doses of 30 mg to 70 mg VYVANSE capsule.

Effect of food on capsule formulation
Neither food (a high fat meal or yogurt) nor orange juice affects the observed AUC and C_{max} of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of VYVANSE capsules. Food prolongs T_{max} by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal or to 4.2 hours with yogurt). After an 8-hour fast, the AUC for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

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

Effect of food on tablet formulation
Administration of 60 mg VYVANSE chewable tablet with food (a high-fat meal) decreases the exposure (C_{max} and AUC_{inf}) of dextroamphetamine by about 5% to 7%, and prolongs mean T_{max} by approximately 1 hour (from 3.9 hours at fasted state to 4.9 hours).

Elimination
Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in volunteers ages 6 years and older. The plasma elimination half-life of dextroamphetamine was approximately 8.6 to 9.5 hours in pediatric patients 6 to 12 years and 10 to 11.3 hours in healthy adults.

Metabolism
Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells after oral administration of lisdexamfetamine dimesylate. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). Lisdexamfetamine is not metabolized by cytochrome P450 enzymes.

Excretion
Following oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine.

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

Figure 1: Specific Populations*:

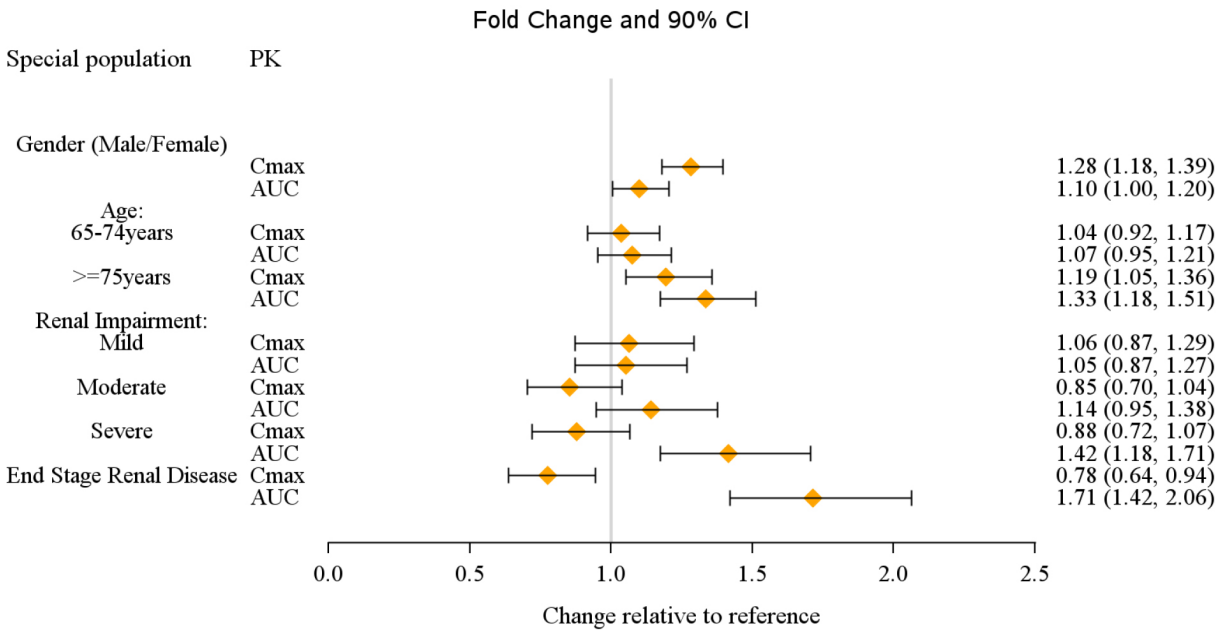
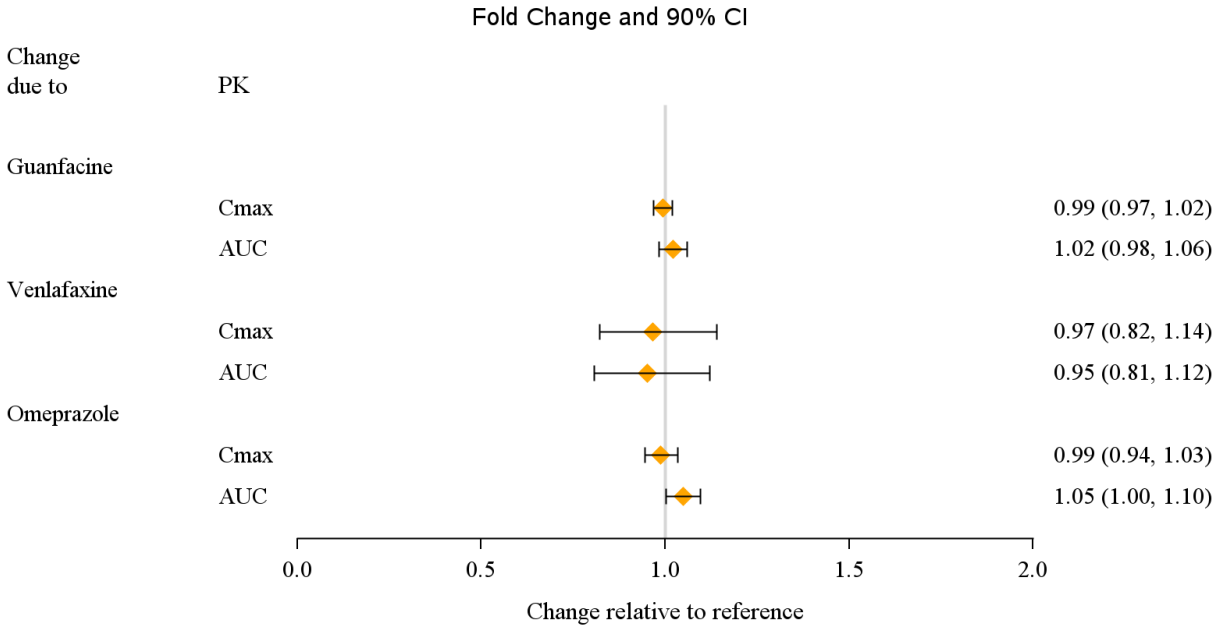


*Figure 1 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

Drug Interaction Studies

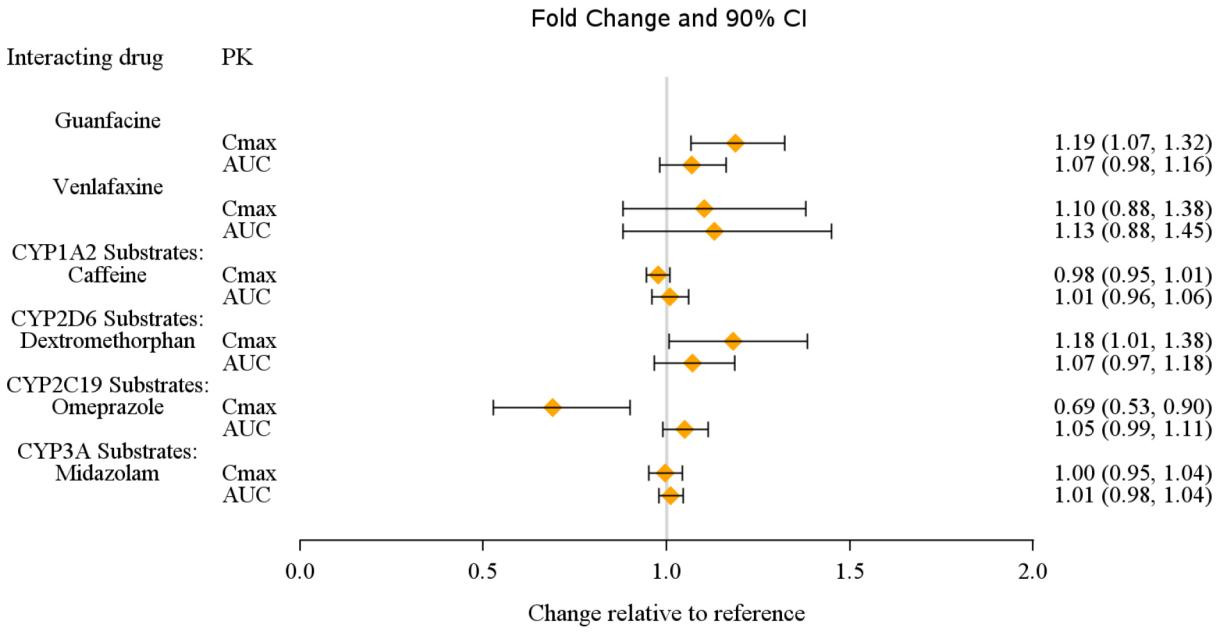
Effects of other drugs on the exposures of dextroamphetamine are summarized in Figure 2.

Figure 2: Effect of Other Drugs on VYVANSE:



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

Figure 3: Effect of VYVANSE on Other Drugs:



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
Carcinogenicity studies of lisdexamfetamine dimesylate have not been performed. No evidence of carcinogenicity was found in studies in which d-, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats.

Mutagenesis
Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK$^{+/-}$ mouse lymphoma assay *in vitro*.

Impairment of Fertility
Amphetamine (d- to l-enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Attention Deficit Hyperactivity Disorder (ADHD)

Pediatric Patients Ages 6 to 12 Years with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 1) was conducted in pediatric patients ages 6 to 12 years (N=290) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of VYVANSE or placebo once daily in the morning for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), an 18-item questionnaire with a score range of 0-54 points that measures the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome. Mean effects at all doses were similar; however, the highest dose (70 mg/day) was numerically superior to both lower doses (Study 1 in Table 6). The effects were maintained throughout the day based on parent ratings (Conners' Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm).

A double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 2) was conducted in pediatric patients ages 6 to 12 years (N=52) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 3-week open-label dose optimization with Adderall XR®, patients were randomly assigned to continue their optimized dose of Adderall XR (10 mg, 20 mg, or 30 mg), VYVANSE (30 mg, 50 mg, or 70 mg), or placebo once daily in the morning for 1 week each treatment. Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose using the Swanson, Kotkin, Agler, M.Flynn, and Pelham Deportment scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures deportment problems leading to classroom disruptions. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS across the 8 assessments were observed between patients when they received VYVANSE compared to patients when they received placebo (Study 2 in Table 6). The drug effect reached statistical significance from hours 2 to 12 post-dose, but was not significant at 1 hour.

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 3) was conducted in pediatric patients ages 6 to 12 years (N=129) who met

DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose optimization with VYVANSE (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue their optimized dose of VYVANSE or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-Deportment scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients when they received VYVANSE compared to patients when they received placebo (Study 3 in Table 6, Figure 4).

Pediatric Patients Ages 13 to 17 Years with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 4) was conducted in pediatric patients ages 13 to 17 years (N=314) who met DSM-IV criteria for ADHD. In this study, patients were randomized in a 1:1:1:1 ratio to a daily morning dose of VYVANSE (30 mg/day, 50 mg/day or 70 mg/day) or placebo for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome (Study 4 in Table 6).

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

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

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

Maintenance of Efficacy Study (Study 6) – A double-blind, placebo-controlled, randomized withdrawal study was conducted in pediatric patients ages 6 to 17 years (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label VYVANSE for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and Total Score on the ADHD-RS ≤22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized

to ongoing treatment with the same dose of VYVANSE (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double-blind phase. A significantly lower proportion of treatment failures occurred among VYVANSE subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase. Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5).

Adults: Short-Term Treatment in ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 7) was conducted in adults ages 18 to 55 (N=420) who met DSM-IV criteria for ADHD. In this study, patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of VYVANSE or placebo for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome (Study 7 in Table 6).

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

Adults: Maintenance Treatment in ADHD

A double-blind, placebo-controlled, randomized withdrawal design study (Study 9) was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV criteria for ADHD. At study entry, patients must have had documentation of treatment with VYVANSE for a minimum of 6 months and had to demonstrate treatment response as defined by Clinical Global Impression Severity (CGI-S) ≤3 and Total Score on the ADHD-RS

<22. ADHD-RS Total Score is a measure of core symptoms of ADHD. The CGI-S score assesses the clinician's impression of the patient's current illness state and ranges from 1 (not at all ill) to 7 (extremely ill). Patients that maintained treatment response at Week 3 of the open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of VYVANSE (N=56) or switched to placebo (N=60) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6-week double-blind phase. The efficacy endpoint was the proportion of patients with treatment failure during the double-blind phase. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind phase. Maintenance of efficacy for patients treated with VYVANSE was demonstrated by the significantly lower proportion of patients with treatment failure (9%) compared to patients receiving placebo (75%) at endpoint during the double-blind phase (Study 9, Figure 7).

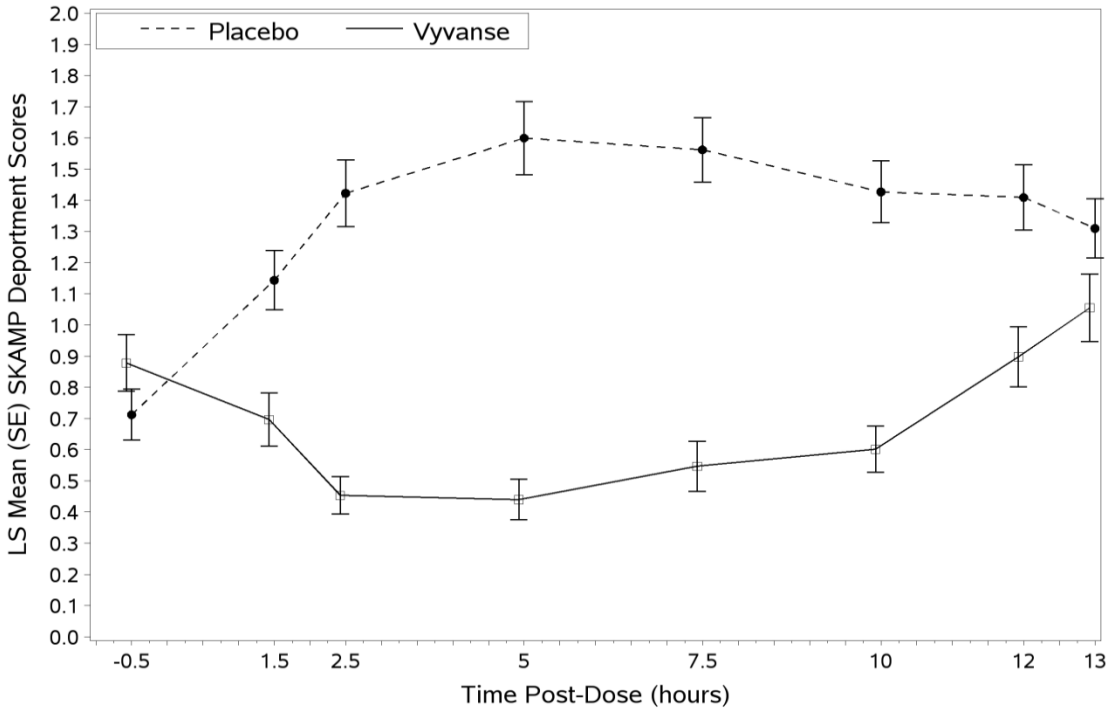
Table 6: Summary of Primary Efficacy Results from Short-term Studies of VYVANSE in Pediatric Patients (Ages 6 to 17) and Adults with ADHD

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1 (6 – 12 years)	ADHD-RS-IV	VYVANSE (30 mg/day)*	43.2 (6.7)	-21.8 (1.6)	-15.6 (-19.9, -11.2)
		VYVANSE (50 mg/day)*	43.3 (6.7)	-23.4 (1.6)	-17.2 (-21.5, -12.9)
		VYVANSE (70 mg/day)*	45.1(6.8)	-26.7 (1.5)	-20.5 (-24.8, -16.2)
		Placebo	42.4 (7.1)	-6.2 (1.6)	--
Study 2 (6 – 12 years)	Average SKAMP-DS	VYVANSE (30, 50 or 70 mg/day)*	-- [b]	0.8 (0.1) [d]	-0.9 (-1.1, -0.7)
		Placebo	-- [b]	1.7 (0.1) [d]	--
Study 3 (6 – 12 years)	Average SKAMP-DS	VYVANSE (30, 50 or 70 mg/day)*	0.9 (1.0)[c]	0.7 (0.1)[d]	-0.7 (-0.9, -0.6)
		Placebo	0.7 (0.9)[c]	1.4 (0.1)[d]	--
Study 4 (13 – 17 years)	ADHD-RS-IV	VYVANSE (30 mg/day)*	38.3 (6.7)	-18.3 (1.2)	-5.5 (-9.0, -2.0)
		VYVANSE (50 mg/day)*	37.3 (6.3)	-21.1 (1.3)	-8.3 (-11.8, -4.8)
		VYVANSE (70 mg/day)*	37.0 (7.3)	-20.7 (1.3)	-7.9 (-11.4, -4.5)
		Placebo	38.5 (7.1)	-12.8 (1.2)	--
Study 5 (6 – 17 years)	ADHD-RS-IV	VYVANSE (30, 50 or 70 mg/day)*	40.7 (7.3)	-24.3 (1.2)	-18.6 (-21.5, -15.7)
		Placebo	41.0 (7.1)	-5.7 (1.1)	--
Study 7 (18 – 55 years)	ADHD-RS-IV	VYVANSE (30 mg/day)*	40.5 (6.2)	-16.2 (1.1)	-8.0 (-11.5, -4.6)
		VYVANSE (50 mg/day)*	40.8 (7.3)	-17.4 (1.0)	-9.2 (-12.6, -5.7)
		VYVANSE (70 mg/day)*	41.0 (6.0)	-18.6 (1.0)	-10.4 (-13.9, -6.9)
		Placebo	39.4 (6.4)	-8.2 (1.4)	--
Study 8 (18 – 55 years)	Average PERMP	VYVANSE (30, 50 or 70 mg/day)*	260.1 (86.2)[c]	312.9 (8.6)[d]	23.4 (15.6, 31.2)
		Placebo	261.4 (75.0)[c]	289.5 (8.6)[d]	--

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.
[b] Pre-dose SKAMP-DS was not collected.
[c] Pre-dose SKAMP-DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.

[d] LS Mean for SKAMP-DS (Study 2 and 3) or PERMP (Study 8) is post-dose average score over all sessions of the treatment day, rather than change from baseline.
* Doses statistically significantly superior to placebo.

Figure 4 LS Mean SKAMP Deportment Subscale Score by Treatment and Time-point for Pediatric Patients Ages 6 to 12 with ADHD after 1 Week of Double-Blind Treatment (Study 3)



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

Figure 5 Kaplan-Meier Estimated Proportion of Patients with Treatment Failure for Pediatric Patients Ages 6 to 17 (Study 6)

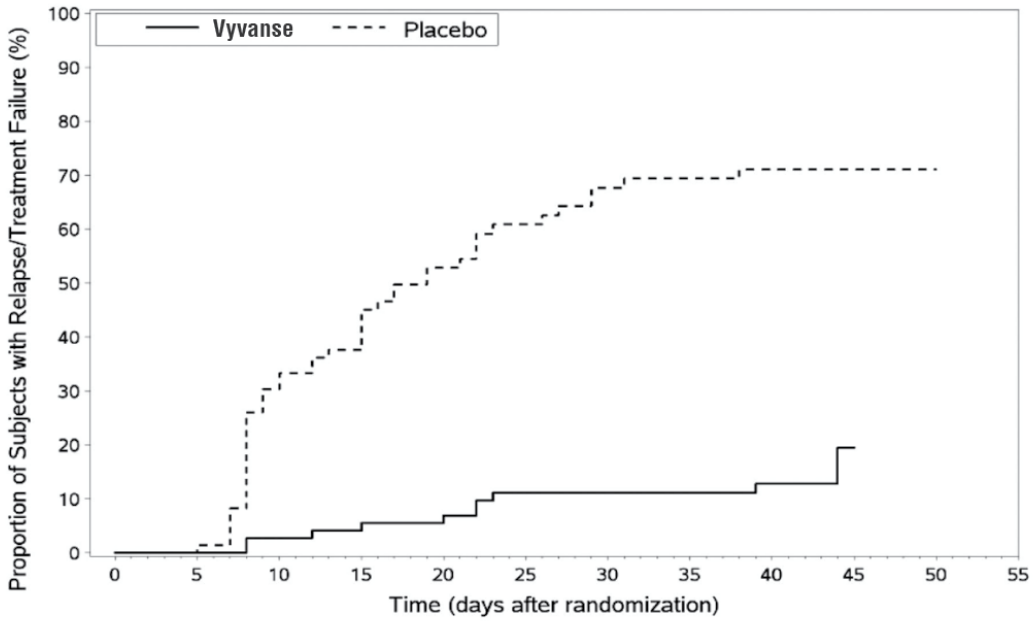
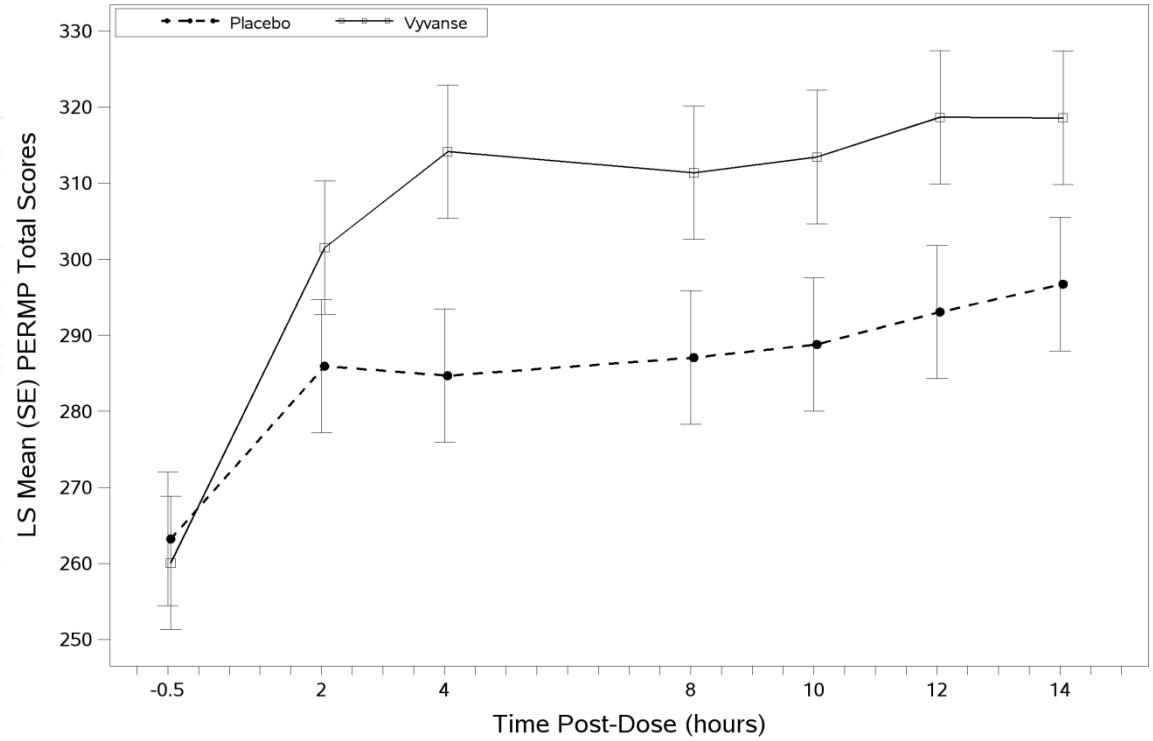
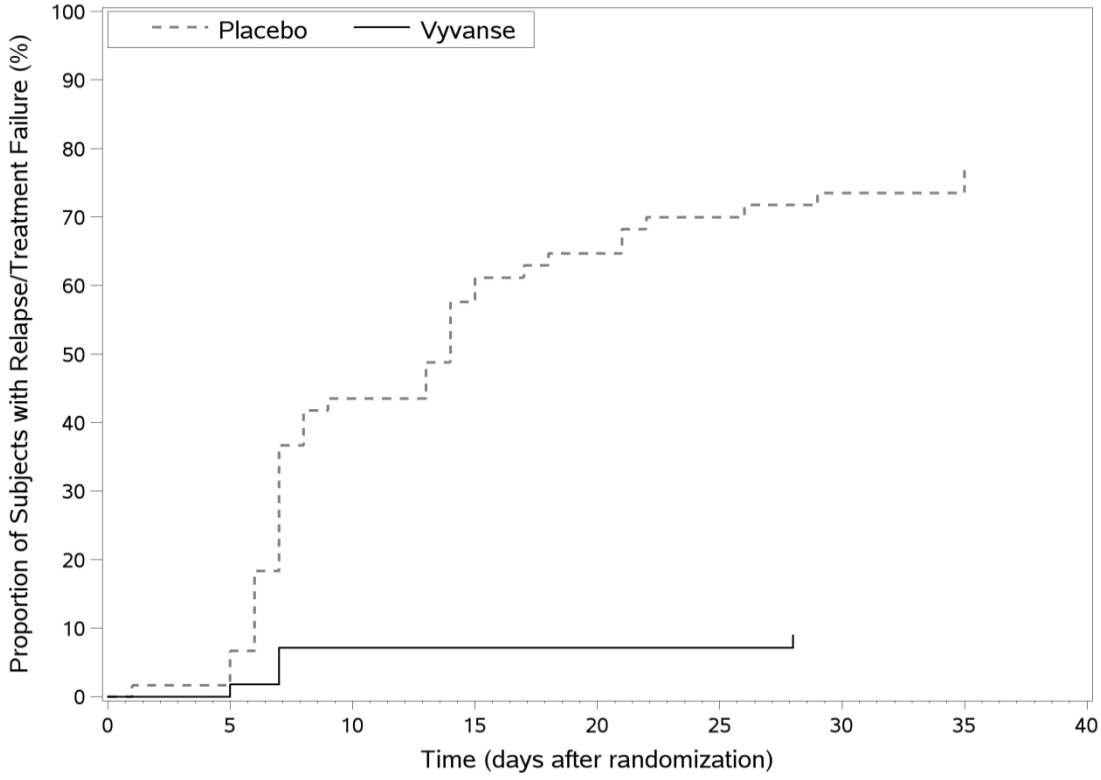


Figure 6 LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double-Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

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



14.2 Binge Eating Disorder (BED)

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

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

Both 12-week studies consisted of a 4-week dose-optimization period and an 8-week dose-maintenance period. During dose-optimization, subjects assigned to VYVANSE began

treatment at the titration dose of 30 mg/day and, after 1 week of treatment, were subsequently titrated to 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 change from baseline at Week 12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit. Subjects from both studies on VYVANSE had a statistically significantly greater reduction from baseline in mean number of binge days per week at Week 12. In addition, subjects on VYVANSE showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score.

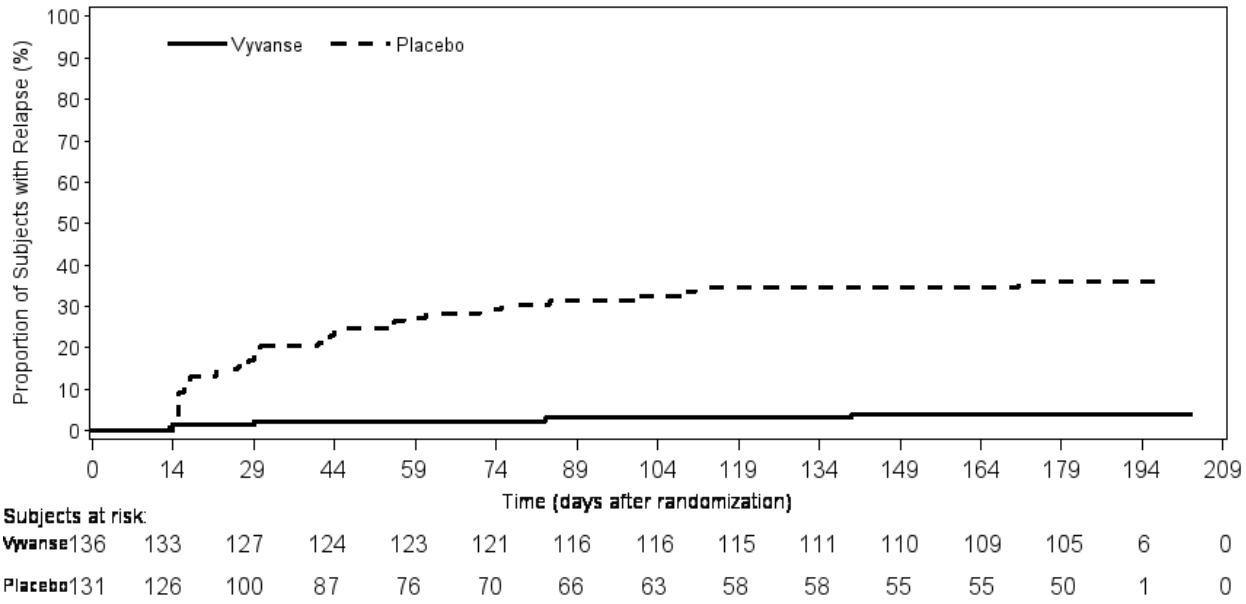
Table 7: Summary of Primary Efficacy Results in BED

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)
Study 11	VYVANSE (50 or 70 mg/day)*	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study 12	VYVANSE (50 or 70 mg/day)*	4.66 (1.27)	-3.92 (0.14)	-1.66 (-2.04, -1.28)
	Placebo	4.82 (1.42)	-2.26 (0.14)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

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

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



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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

*VYVANSE (*lisdexamfetamine dimesylate*) capsules:*

- VYVANSE capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg), bottles of 100, NDC 59417-101-10
- VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10
- VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10
- VYVANSE capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10
- VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10
- VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10
- VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417-107-10

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

- 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, NDC 59417-115-01
- 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, NDC 59417-116-01
- 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, NDC 59417-117-01
- 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, NDC 59417-118-01
- 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, NDC 59417-119-01
- 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, NDC 59417-120-01

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP.

Store at room temperature, 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Abuse, Misuse, and Addiction
Educate patients and their families about the risks of abuse, misuse, and addiction of VYVANSE, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), Overdosage (10)]*. Advise patients to store VYVANSE in a safe place, preferably locked, and instruct patients to not give VYVANSE to anyone else.

Risks to Patients with Serious Cardiac Disease
Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with VYVANSE use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate
Instruct patients that VYVANSE can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects.

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

Long-Term Suppression of Growth in Pediatric Patients
Advise patients that VYVANSE may cause slowing of growth including weight loss *[see Warnings and Precautions (5.5)]*.

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]
Instruct patients beginning treatment with VYVANSE about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes. Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking VYVANSE. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome with concomitant use of VYVANSE and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid *[see Contraindications (4), Warnings and Precautions (5.7) and Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Concomitant Medications
Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions *[see Drug Interactions (7.1)]*. Advise patient or caregiver of steps to take with VYVANSE when a laboratory imaging procedure is ordered *[see Drug Interactions (7.2)]*.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome
Advise patients that motor and verbal tics and worsening of Tourette's Syndrome may occur during treatment with VYVANSE. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.8)]*.

Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VYVANSE during pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy

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

Lactation

Advise women not to breastfeed if they are taking VYVANSE *[see Use in Specific Populations (8.2)]*.

Administration Instructions

- Capsules: Advise patients to take the capsules whole or empty and mix the entire contents with yogurt, water, or orange juice. Advise patients to consume the mixture immediately and not to store for future use *[see Dosage and Administration (2.2)]*.
- Chewable tablets: Advise patients that chewable tablets must be chewed thoroughly before swallowing *[see Dosage and Administration (2.2)]*.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

For more information call 1-800-828-2088

MEDICATION GUIDE
VYVANSE® (Vi – vans)
(lisdexamfetamine dimesylate)
capsules and chewable tablets, CII

What is the most important information I should know about VYVANSE?
VYVANSE may cause serious side effects, including:

- **Abuse, misuse, and addiction.** VYVANSE has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of VYVANSE, other amphetamine containing medicines, and methylphenidate containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of VYVANSE or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with VYVANSE and will monitor you or your child during treatment.
  - VYVANSE may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
  - Do not give VYVANSE to anyone else. See "**What is VYVANSE?**" for more information.
  - Keep VYVANSE in a safe place and properly dispose of any unused medicine. See "**How should I store VYVANSE?**" for more information.
  - Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease. Your healthcare provider should check you or your child carefully for heart problems before starting treatment with VYVANSE. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.
  Call your healthcare provider right away or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with VYVANSE.
- **Increased blood pressure and heart rate**. Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with VYVANSE.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

  Tell your healthcare provider about any mental problems you or your child have or about a family history of suicide, bipolar illness, or depression.
  Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with VYVANSE, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is VYVANSE?
VYVANSE is a central nervous system (CNS) stimulant prescription medicine used for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years of age and older. VYVANSE may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
- Moderate to severe binge eating disorder (BED) in adults. VYVANSE may help reduce the number of binge eating days in people with BED.

VYVANSE is not recommended for use in children under 6 years of age with ADHD.

VYVANSE is not for weight loss. It is not known if VYVANSE is safe and effective for the treatment of obesity.

It is not known if VYVANSE is safe and effective for use in children with BED.

VYVANSE is a federally controlled substance (CII) because it contains lisdexamfetamine dimesylate that can be a target for people who abuse prescription medicines or street drugs. Keep VYVANSE in a safe place to protect it from theft. Never give your VYVANSE to anyone else because it may cause death or harm them. Selling or giving away VYVANSE may harm others and is against the law.

Who should not take VYVANSE?
Do not take VYVANSE if you or your child are:

- allergic to amphetamine products or any of the ingredients in VYVANSE. See the end of this Medication Guide for a complete list of ingredients in VYVANSE.

- taking, or have stopped taking in the last 14 days, a medicine called a Monoamine Oxidase Inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue.

Before taking VYVANSE, tell your healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure, or have a family history of sudden death or heart problems
- have mental problems including psychosis, mania, bipolar illness, or depression or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- have kidney problems
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. VYVANSE may harm the unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with VYVANSE.
  - There is a pregnancy registry for females who are exposed to VYVANSE during pregnancy. The purpose of the registry is to collect information about the health of females exposed to VYVANSE and their baby. If you or your child becomes pregnant during treatment with VYVANSE, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visit online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/adhd-medications/.
- are breastfeeding or plan to breastfeed. VYVANSE passes into breast milk. You should not breastfeed during treatment with VYVANSE. Talk to your healthcare provider about the best way to feed the baby during treatment with VYVANSE.

Tell your healthcare provider about all the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VYVANSE can affect the way other medicines work, and other medicines may affect how VYVANSE works. Taking VYVANSE with other medicines can cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with VYVANSE.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Keep a list of all medicines to show your healthcare provider and pharmacist when you get a new medicine. Your healthcare provider will decide if VYVANSE can be taken with other medicines.

Do not start any new medicine during treatment with VYVANSE without talking to your healthcare provider first.

Your healthcare provider may tell you to stop taking VYVANSE for a short time before you get certain imaging tests because VYVANSE may impact the results of some tests.

How should VYVANSE be taken?

- Take VYVANSE exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take VYVANSE 1 time each day in the morning with or without food.
- Taking VYVANSE in the afternoon may cause trouble sleeping.
- VYVANSE comes in capsules or chewable tablets.

  Taking VYVANSE capsules:
  - Swallow VYVANSE capsules whole.
  - If VYVANSE capsules cannot be swallowed whole, the capsule may be opened and the entire contents sprinkled onto yogurt, or poured into water or orange juice.
    - Using a spoon, break apart any powder that is stuck together. Stir the VYVANSE powder and yogurt, water, or orange juice until they are completely mixed together.
    - Swallow all the yogurt, water, or orange juice mixture right away. **Do not** store the yogurt, water, or orange juice mixture.
    - It is normal to see a filmy coating on the inside of your glass or container after you eat or drink all the VYVANSE mixture.

Taking VYVANSE chewable tablets:

- Chew VYVANSE tablets completely before swallowing.

If you or your child take too much VYVANSE, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of VYVANSE?

VYVANSE may cause serious side effects, including:

- See **"What is the most important information I should know about VYVANSE?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with VYVANSE. VYVANSE treatment may be stopped if your child is not growing or gaining weight as expected.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon).** Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you or your child have numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

  Call your healthcare provider right away if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with VYVANSE.
- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome may happen when VYVANSE is taken with certain other medicines. Stop taking VYVANSE and call your healthcare provider or go to the nearest hospital emergency room right away if you or your child develop any of the following signs and symptoms of serotonin syndrome:
  - agitation
  - flushing
  - coma
  - loss of coordination
  - dizziness
  - seeing or hearing things that are not real (hallucination)
  - high body temperature (hyperthermia)
  - fast heartbeat
  - seizures
  - sweating
  - confusion
  - tremors, stiff muscles, or muscle twitching
  - changes in blood pressure
  - nausea, vomiting, diarrhea
- **New or worsening tics or worsening Tourette's syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with VYVANSE.

The most common side effects of VYVANSE in children 6 to 17 years old and adults with ADHD include:

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

The most common side effects of VYVANSE in adults with BED include:

- dry mouth
- decreased appetite
- constipation
- anxiety
- trouble sleeping
- increased heart rate
- feeling jittery

These are not all the possible side effects of VYVANSE.

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

How should I store VYVANSE?

- Store VYVANSE in a safe place (like a locked cabinet) at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container tightly closed and protect VYVANSE from light.
- Dispose of remaining, unused, or expired VYVANSE by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix VYVANSE with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away VYVANSE in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep VYVANSE and all medicines out of the reach of children.

General information about the safe and effective use of VYVANSE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VYVANSE for a condition for which it was not prescribed. Do not give VYVANSE to other people, even if they have the same symptoms that you have. It may harm them and it is against the law. You can ask your pharmacist or healthcare provider for information about VYVANSE that is written for health professionals.

What are the ingredients in VYVANSE?

Active ingredient: lisdexamfetamine dimesylate

Capsule inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells (imprinted with S489) contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide.

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

Distributed by: Takeda Pharmaceuticals America, Inc., Cambridge, MA 02142.

For more information, go to www.vyvanse.com or call 1-800-828-2088.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2026

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MYDAYIS safely and effectively. See full prescribing information for MYDAYIS.

MYDAYIS® (mixed salts of a single-entity amphetamine product) extended-release capsules, for oral use, CII
Initial U.S. Approval: 2001

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

MYDAYIS has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including MYDAYIS, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing MYDAYIS, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

INDICATIONS AND USAGE

MYDAYIS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older. (1)

Limitations of Use:
Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite. (8.4)

DOSAGE AND ADMINISTRATION

- MYDAYIS should be administered once daily upon awakening.

-	Recommended Starting Dose	Titration Schedule	Maximum Daily Dose
Adults	12.5 mg	12.5 mg weekly	50 mg
Pediatrics (13 to 17)	12.5 mg	12.5 mg weekly	25 mg

- In adult patients with severe renal impairment the maximum dose should not exceed 25 mg daily. Use in adult patients with ESRD is not recommended. (2.6, 8.6)
- The maximum dose in pediatric patients with severe renal impairment is 12.5 mg daily. Use in pediatric patients with ESRD is not recommended. (2.6, 8.6)
- Patients are advised to take consistently either with or without food. (2.2)
- Administer upon awakening because the effects may last up to 16 hours and there is the potential for insomnia. (2.2)
- Prior to treatment, assess for presence of cardiac disease. (2.1)
- To avoid substitution errors and overdosage, do not substitute for other amphetamine products on a milligram-per-milligram basis because of different amphetamine base compositions and differing pharmacokinetic profiles. (2.7)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in MYDAYIS. (4)
- Use with monoamine oxidase (MAO) inhibitors, or within 14 days of the last MAO inhibitor dose. (4, 7.1)

WARNINGS AND PRECAUTIONS

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease. (5.2)
- Increased Blood Pressure and Heart Rate: Monitor blood pressure and pulse. (5.3)
- Psychiatric Adverse Reactions: Prior to initiating MYDAYIS, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing MYDAYIS. (5.4)
- Long-Term Suppression of Growth in Pediatric Patients: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.5)
- Peripheral Vasculopathy, Including Raynaud's Phenomenon: Careful observation for digital changes is necessary during MYDAYIS treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- Seizures: May lower the convulsive threshold. If a seizure occurs, discontinue MYDAYIS. (5.7)
- Serotonin Syndrome: Increased risk when coadministered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue MYDAYIS and initiate supportive treatment. (5.8)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating MYDAYIS, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.10)

ADVERSE REACTIONS

Most common adverse reactions in patients with ADHD (incidence ≥5% and at a rate at least twice placebo) are:

- Pediatrics (13 years and older): insomnia, decreased appetite, decreased weight, irritability, and nausea. (6.1)
- Adults: insomnia, decreased appetite, decreased weight, dry mouth, increased heart rate, and anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Acidifying and Alkalinizing Agents: Agents that alter GI and urinary pH can alter blood levels of amphetamine. Acidifying agents (GI and urinary) decrease amphetamine blood levels, while alkalinizing agents (GI and urinary) increase amphetamine blood levels. Adjust MYDAYIS dosage accordingly. (2.5, 7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Pediatric: Safety and effectiveness have not been established in pediatric patients ages 12 years and younger. (8.4)
- Renal Impairment: Dose adjustment is needed in patients with severe renal insufficiency. Use of MYDAYIS in patients with ESRD is not recommended. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

MYDAYIS® has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including MYDAYIS, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing MYDAYIS, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout MYDAYIS treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

MYDAYIS is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older *[see Clinical Studies (14)]*.

Limitations of Use:
Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose, and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with MYDAYIS, assess:

- for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating MYDAYIS *[see Warnings and Precautions (5.10)]*

2.2 General Administration Information

Because the effects of MYDAYIS may last up to 16 hours and there is potential for insomnia, administer once daily in the morning upon awakening. In the event of a missed dose, do not administer later in the day. Do not administer additional medication to make up for the missed dose *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

2.3 Administration Instructions

Administer MYDAYIS orally with or without food. Advise patients to take MYDAYIS consistently either with food or without food *[see Clinical Pharmacology (12.3)]*.

MYDAYIS may be administered in one of the following ways:

- Swallow MYDAYIS capsules whole, or
- Open capsule and sprinkle the entire contents over a spoonful of applesauce. The sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the sprinkled applesauce in its entirety without chewing.
- The dose of a single capsule should not be divided.

2.4 Recommended Dosage

Adults (18 to 55 years)

The recommended starting dose of MYDAYIS is 12.5 mg once daily in the morning upon awakening. Initial doses of 25 mg once daily may be considered for some patients. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly, up to a maximum dose of 50 mg once daily, based on the therapeutic needs and response of the patient. Doses above 50 mg daily have shown no additional clinically meaningful benefit.

Pediatric Patients (13 to 17 years)

The recommended starting dose is 12.5 mg once daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly, up to a recommended maximum dose of 25 mg once daily. The dose should be individualized according to the needs and response of the patient. Doses higher than 25 mg have not been evaluated in clinical trials in pediatric patients.

2.5 Dosage Modifications Due to Drug Interactions

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

2.6 Dosage in Patients with Renal Impairment

In adult patients with severe renal impairment (GFR between 15 to <30 mL/min/1.73 m^2), the recommended starting dose of MYDAYIS is 12.5 mg daily with a maximum recommended dose of 25 mg daily. MYDAYIS is not recommended for use in patients with end stage renal disease (ESRD <15 mL/min/1.73 m^2). In pediatric patients (13 to 17 years) with severe renal impairment, the maximum dose is 12.5 mg, if tolerated *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.7 Switching From Other Amphetamine Products

For patients switching from another medication or any other amphetamine products, discontinue that treatment, and titrate with MYDAYIS using the titration schedule *[see Dosage and Administration (2.4)]*.

Do not substitute for other amphetamine products on a milligram-per-milligram basis because of different amphetamine base compositions and differing pharmacokinetic profiles *[see Warnings and Precautions (5.9), Description (11), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- Extended-release capsules 12.5 mg: green body/green cap (imprinted with SHIRE 465 and 12.5 mg)
- Extended-release capsules 25 mg: ivory body/green cap (imprinted with SHIRE 465 and 25 mg)
- Extended-release capsules 37.5 mg: ivory body/light caramel cap (imprinted with SHIRE 465 and 37.5 mg)
- Extended-release capsules 50 mg: ivory body/purple cap (imprinted with SHIRE 465 and 50 mg)

4 CONTRAINDICATIONS

MYDAYIS is contraindicated in patients with:

- Known hypersensitivity to amphetamine, or other components of MYDAYIS. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products *[see Adverse Reactions (6.2)]*.

- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

MYDAYIS has a high potential for abuse and misuse. The use of MYDAYIS exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. MYDAYIS can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2)]*. Misuse and abuse of CNS stimulants, including MYDAYIS, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing MYDAYIS, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store MYDAYIS in a safe place, preferably locked, and instruct patients to not give MYDAYIS to anyone else. Throughout MYDAYIS treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage.

Avoid MYDAYIS use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mmHg) and heart rate (mean increase about 3 to 6 bpm). Some patients may have larger increases.

Monitor all MYDAYIS-treated patients for potential tachycardia and hypertension *[see Adverse Reactions (6.1)]*.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating MYDAYIS treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms

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

5.5 Long-Term Suppression of Growth in Pediatric Patients

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

In a 4 week, placebo-controlled trial of MYDAYIS in patients ages 6 to 17 years old with ADHD, there was a decrease in weight in the MYDAYIS groups compared to weight gain in the placebo group *[see Adverse Reactions (6.1)]*.

Closely monitor growth (weight and height) in MYDAYIS-treated pediatric patients. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted. MYDAYIS is not approved for use in pediatric patients 12 years and younger *[see Use in Specific Populations (8.4)]*.

5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon

CNS stimulants, including MYDAYIS, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during MYDAYIS treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for MYDAYIS-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.7 Seizures

MYDAYIS may lower the convulsive threshold in patients with prior history of seizure, in patients with prior EEG abnormalities in the absence of seizures, and in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, MYDAYIS should be discontinued.

5.8 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see Drug Interactions (7.1)]*. The coadministration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to MYDAYIS. In these situations, consider an alternative nonserotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (7.1)]*.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

Discontinue treatment with MYDAYIS and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of MYDAYIS with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate MYDAYIS with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

5.9 Potential for Overdose Due to Medication Errors

Medication errors, including substitution and dispensing errors, between MYDAYIS and other amphetamine products could occur, leading to possible overdosage. To avoid substitution errors and overdosage, do not substitute for other amphetamine products on a milligram-per-milligram basis

because of different amphetamine base compositions and differing pharmacokinetic profiles *[see Dosage and Administration (2.7), Overdosage (10)]*.

5.10 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including amphetamine, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating MYDAYIS, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor MYDAYIS-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Hypersensitivity to amphetamine products or other ingredients of MYDAYIS *[see Contraindications (4)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[see Contraindications (4), Drug Interactions (7.1)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, Including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Seizures *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

MYDAYIS was studied in adults (18 to 55 years) and pediatric patients (13 to 17 years) who met Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th editions (DSM-IV-TR® or DSM-5) criteria for ADHD. The safety data for adults were pooled from three randomized, double-blind, placebo-controlled studies in doses of 12.5 mg to 75 mg per day (1.5 times the maximum recommended dosage). Doses higher than 50 mg per day did not demonstrate additional clinical benefit and are not recommended.

The safety data for pediatric patients (13 to 17 years) is from 1 randomized, double-blind, placebo-controlled study of doses of 12.5 mg to 25 mg. The total exposure in patients treated with MYDAYIS totalled 704; this included pediatric patients, 78 adolescent patients and 626 adult patients from multiple well-controlled trials. The duration of use ranged from 4 to 7 weeks *[see Clinical Studies (14)]*.

Adverse Reactions Leading to Discontinuation of Treatment

In pooled controlled trials of adult patients, 9% (54/626) of MYDAYIS-treated patients discontinued

due to adverse reactions compared to 2% (7/328) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (i.e., leading to discontinuation in at least 1% of MYDAYIS-treated patients and at a rate at least twice that of placebo) were insomnia (2%, n=15), blood pressure increased (2%, n=10), decreased appetite (1%, n=5), and headache (1%, n=4).

In a controlled trial including adolescent patients (13 to 17 years), 5% (4/78) of MYDAYIS-treated patients discontinued due to adverse reactions compared to 0% (0/79) of placebo-treated patients. The most frequent adverse reaction leading to discontinuation (i.e., leading to discontinuation in at least 1% of MYDAYIS-treated patients and at a rate at least twice that of placebo) were dizziness (1%, n=1), depression (1%, n=1), abdominal pain upper (1%, n=1), and viral infection (1%, n=1).

Adverse Reactions Occurring at an Incidence of ≥2% and at Least Twice Placebo Among MYDAYIS-Treated Adults in Clinical Trials

The most common adverse reactions reported in adults were insomnia, decreased appetite, dry mouth, decreased weight, heart rate increased, and anxiety. *Table 1* lists the adverse reactions that occurred ≥2% compared to placebo. The most common adverse reaction (insomnia) generally occurred early during treatment with MYDAYIS.

Table 1: Adverse Reactions Reported by 2% or More of Adults Taking MYDAYIS and at Least Twice the Incidence in Patients Taking Placebo in 3 Clinical Trials (4, 6, and 7 Weeks)

Body System	Adverse Reaction	MYDAYIS* (N = 626)	Placebo (N = 328)
Nervous System			
-	Anxiety	7%	3%
-	Feeling Jittery	2%	1%
-	Agitation	2%	0%
-	Bruxism	2%	0%
Psychiatric Disorders			
-	Insomnia	31%	8%
-	Depression	3%	0%
Metabolism and Nutritional Disorders			
-	Decreased Appetite	30%	4%
-	Weight Decreased	9%	0%
Gastrointestinal System			
-	Dry Mouth	23%	4%
-	Diarrhea	3%	1%
Cardiovascular System			
-	Heart Rate Increased	9%	0%
-	Palpitations	4%	2%
Genitourinary System			
-	Dysmenorrhea[a]	4%	2%
-	Erectile Dysfunction[b]	2%	1%

* Includes doses up to 75 mg (1.5 times the maximum recommended dosage).

[a] Dysmenorrhea was observed in 11 females.

[b] Erectile dysfunction was observed in 6 males.

Adverse Reactions Occurring at an Incidence of 2% or More and at Least Twice Placebo Among MYDAYIS-Treated Adolescents (13 to 17 years) in a 4 Week Clinical Trial

The most common adverse reactions reported in adolescents were decreased appetite, nausea, insomnia, abdominal pain upper, irritability, and weight decreased. *Table 2* lists the adverse reactions that occurred ≥2% compared to placebo.

Table 2: Adverse Reactions Reported by ≥2% or More of Adolescents Taking MYDAYIS and at Least Twice the Incidence in Patients Taking Placebo in a 4 Week Clinical Trial

Body System	Adverse Reaction	MYDAYIS (N = 78)	Placebo (N = 79)
Nervous System			
-	Dizziness	4%	0%
Metabolism and Nutrition Disorders			
-	Decreased appetite	22%	6%
-	Weight decreased	5%	1%
Psychiatric Disorders			
-	Irritability	6%	3%
-	Insomnia*	8%	3%
Gastrointestinal Disorders			
-	Nausea	8%	4%
-	Abdominal pain upper	4%	1%

* Insomnia includes terms: initial insomnia, middle insomnia, terminal insomnia and insomnia.

6.2 Adverse Reactions Associated with the Use of Amphetamines

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

Allergic: Urticaria, rash, hypersensitivity reactions, including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Cardiovascular: Dyspnea, sudden death. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, euphoria, dyskinesia, dysphoria, headache, tics, fatigue, aggression, anger, logorrhea, dermatillomania, and paresthesia (including formication), motor and verbal tics.

Endocrine: Impotence, changes in libido, frequent or prolonged erections.

Eye Disorders: Mydriasis.

Gastrointestinal: Unpleasant taste, constipation, intestinal ischemia.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Skin: Alopecia.

Vascular Disorders: Raynaud's phenomenon.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 3: Drugs Having Clinically Important Interactions with Amphetamines

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer MYDAYIS during or within 14 days following the administration of MAOI *[see Contraindications (4)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of amphetamines and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during MYDAYIS initiation or dosage increase. If serotonin syndrome occurs, discontinue MYDAYIS and concomitant serotonergic drug(s) *[see Warnings and Precautions (5.8)]*.
Alkalinizing Agents	
Clinical Impact	May increase exposure to amphetamine and exacerbate the action of amphetamine.
Intervention	Caution should be taken when coadministering MYDAYIS and gastrointestinal and urinary alkalinizing agents.
Acidifying Agents	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose of MYDAYIS based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust MYDAYIS dose or use alternative therapy based on clinical response.
CYP2D6 Inhibitors	
Clinical Impact	May increase the exposure of amphetamine.
Intervention	Start with lower doses and monitor frequently and adjust MYDAYIS dose or use alternative therapy based on clinical response.
Gastric pH Modulators	
Clinical Impact	Potential change in shape of PK profile and exposure may occur.
Intervention	Monitor patients for changes in clinical effect and use alternative therapy based on clinical response.

7.2 Interference with Laboratory Tests

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

Allow for an adequate washout period between administration of MYDAYIS and radioactive diagnostic agents used for dopamine transporter (DAT) visualization. MYDAYIS can interfere with the test results of a radioactive diagnostic agent (ioflupane I-123) that is used for DAT visualization by binding and internalization of the DAT, which may result in lower DAT in the striatum. This may lead to false-positive diagnostic results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to MYDAYIS during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/.

Risk Summary

The limited available data from published literature and postmarketing reports on use of amphetamine in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines *[see Clinical Considerations]*.

In an embryofetal development study, amphetamine (d- to l- enantiomer ratio of 3:1, the same as in MYDAYIS) had no effects on embryofetal morphological development or survival when administered to pregnant rats and rabbits throughout the period of organogenesis up to doses 10 times the maximum recommended human dose (MRHD) of 25 mg/day given to adolescents, on a mg/m^2 body surface area basis. However, in a pre- and postnatal development study, amphetamine (d- to l- ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *[see Data]*.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as MYDAYIS, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

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

Data

Animal Data

Amphetamine (d- to l- enantiomer ratio of 3:1, the same as in MYDAYIS) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 2 and 10 times, respectively, the maximum recommended human

dose (MRHD) of 25 mg/day given to adolescents, on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 8 times the MRHD given to adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A pre- and postnatal development study was conducted with amphetamine (d- to l- enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation Day 6 to lactation Day 20. These doses are approximately 0.6, 2, and 3 times the MRHD of 25 mg/day amphetamine (d- to l- ratio of 3:1) given to adolescents, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on Day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of MYDAYIS in pediatric patients with ADHD ages 13 to 17 years have been established in two placebo-controlled clinical studies *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]*.

The safety and effectiveness of MYDAYIS have not been established in pediatric patients ages 12 years and younger.

MYDAYIS has been studied for the treatment of ADHD in pediatric patients 6 to 12 years in two placebo controlled safety and efficacy trials. In the first trial, pediatric patients 6 to 12 years experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including higher rates of insomnia (30% vs 8%) and appetite decreased (43% vs 22%). In addition, amphetamine systemic exposures (both d- and l-) in pediatric patients 6 to 12 years following a single dose were higher than those observed in adults at the same dose (72 to 79% higher C_{max} and approximately 83% higher AUC). A second trial evaluated a lower dose than those approved for pediatric patients 13 to 17 years; efficacy was not demonstrated for the lower dose. Therefore, a safe and effective dose cannot be established in pediatric patients 12 years and younger.

Growth Suppression

Growth should be monitored during treatment with stimulants, including MYDAYIS, in pediatric patients 13 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Juvenile Animal Toxicity Data

Juvenile rats treated with mixed amphetamine salts (same as in MYDAYIS) early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 8 times the maximum recommended human dose (MRHD) given to children on a mg/m^2 basis. No recovery was seen following a drug-free period. A delay in sexual maturation was observed at a dose approximately 8 times the MRHD given to children on a mg/m^2 basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1, the same as in MYDAYIS) of 2, 6, or 20 mg/kg on days 7 to 13 of age; from Day 14 to approximately Day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.8, 2, and 8 times the MRHD of 25 mg/day given to children on a mg/m^2 basis. Postdosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

8.5 Geriatric Use

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

8.6 Renal Impairment

Due to reduced clearance of amphetamine in patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73 m^2), the maximum dose in adults should be reduced. Pediatric patients ages 13 to 17 years with severe renal insufficiency can be given the recommended starting dose if tolerated, but the dose should not be escalated. MYDAYIS is not recommended in patients with ESRD (GFR <15 mL/min/1.73 m^2) *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

D-amphetamine is not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

MYDAYIS contains mixed amphetamine salts, a Schedule II controlled substance.

9.2 Abuse

MYDAYIS has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. MYDAYIS can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of amphetamine may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including MYDAYIS, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

9.3 Dependence

Physical Dependence

MYDAYIS may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including MYDAYIS include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

MYDAYIS may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of MYDAYIS should be considered when treating patients with overdose. D-amphetamine is not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

MYDAYIS extended-release capsules contain mixed salts of a single-entity amphetamine, a CNS stimulant. MYDAYIS contains equal amounts (by weight) of four salts: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate. This results in a 3:1 mixture of dextro- to levo- amphetamine base equivalent.

The 12.5 mg, 25 mg, 37.5 mg, and 50 mg strength capsules are for oral administration. They contain three types of drug-releasing beads, an immediate release and two different types of delayed release (DR) beads. The first DR bead releases amphetamine at pH 5.5 and the other DR bead releases amphetamine at pH 7.0.

	CAPSULE STRENGTHS			
EACH CAPSULE CONTAINS:	**12.5 mg**	**25 mg**	**37.5 mg**	**50 mg**
Dextroamphetamine Saccharate	3.125 mg	6.250 mg	9.375 mg	12.500 mg
Amphetamine Aspartate Monohydrate	3.125 mg	6.250 mg	9.375 mg	12.500 mg
Dextroamphetamine Sulfate	3.125 mg	6.250 mg	9.375 mg	12.500 mg
Amphetamine Sulfate	3.125 mg	6.250 mg	9.375 mg	12.500 mg
Total mixed amphetamine salts	12.500 mg	25 mg	37.5 mg	50 mg
Total amphetamine base equivalence	7.8 mg	15.6 mg	23.5 mg	31.3 mg

Inactive Ingredients and Colors

The inactive ingredients in MYDAYIS capsules include: hard gelatin capsules, ethylcellulose, hydroxypropyl methylcellulose, methacrylic acid copolymer, methyl acrylate, methyl methacrylate, methacrylic acid copolymer, Opadry® beige, sugar spheres, talc, and triethyl citrate. The gelatin capsules for all four strengths contain gelatin, titanium dioxide, yellow iron oxide, and edible inks. The 12.5 mg and 25 mg strength gelatin capsules also contain FD&C Blue #2. The 37.5 mg strength also contains red iron oxide. The 50 mg strength capsule also contains D&C Red #28, D&C Red #33, and FD&C Blue #1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

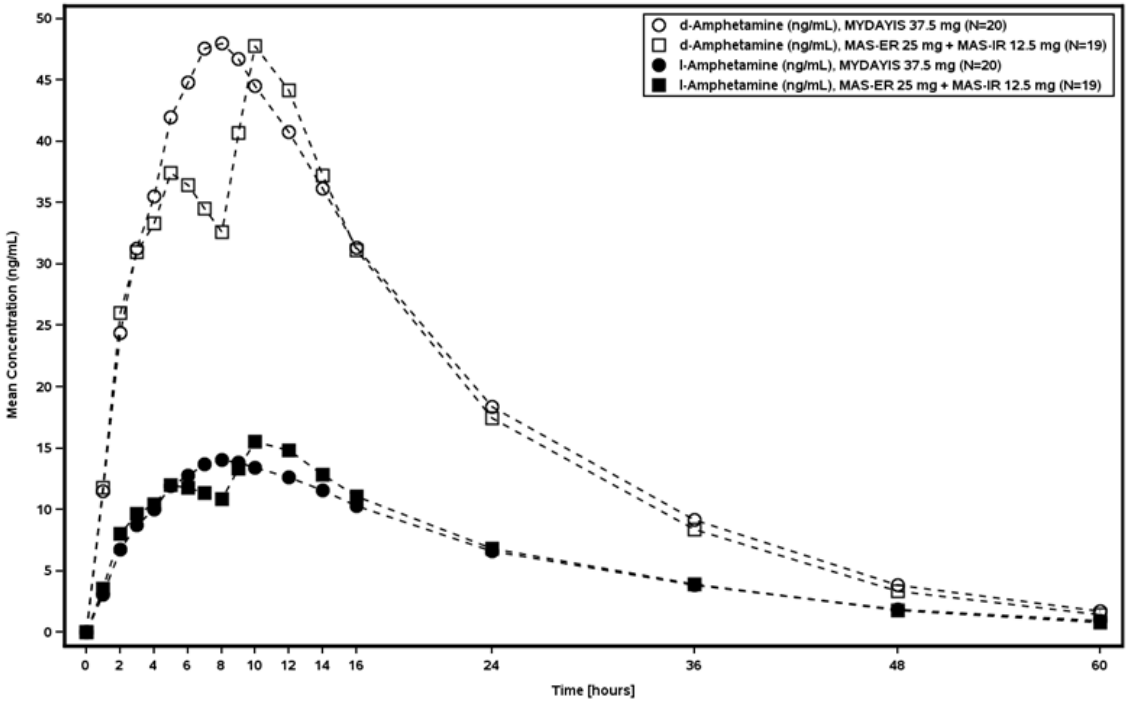
12.3 Pharmacokinetics

MYDAYIS contains d-amphetamine and l-amphetamine salts in the ratio of 3:1. Pharmacokinetic studies of d- and l-amphetamine after oral administration of MYDAYIS have been conducted in healthy adults (19 to 52 years) and pediatric patients (6 to 17 years) with ADHD. Following administration of MYDAYIS, the peak plasma concentrations occurred in about 7 to 10 hours in pediatric patients and about 8 hours in adults for both d-amphetamine and l-amphetamine. The mean plasma elimination half-life for d-amphetamine ranges from about 10 to 11 hours and l-amphetamine from 10 to 13 hours in both pediatric and adult patients.

Absorption

MYDAYIS exhibits linear dose proportionality over the range of 12.5 to 50 mg. Steady-state is achieved between Days 7 and 8 of dosing with mean accumulation ratio of 1.6. A single dose of MYDAYIS 37.5 mg capsules provided comparable plasma concentration profiles of both d- and l-amphetamine to mixed amphetamine salts extended release (MAS-ER) 25 mg followed by 12.5 mg immediate release amphetamine administered 8 hours later *(Figure 1)*.

Figure 1: Mean Plasma Concentrations of d- and l-amphetamine Following Oral Administration of MYDAYIS 37.5 mg vs MAS-ER 25 mg Followed by Immediate-Release MAS-IR 12.5 mg 8 Hours Later in Adults



Effect of Food

High fat meal does not affect the extent of absorption of d- and l-amphetamine when taken with MYDAYIS. T_{max} is prolonged by 5 hours (from 7.0 hours at fasted state to 12.0 hours after a high-fat meal) for d-amphetamine and 4.5 hours (from 7.5 hours at fasted state to 12 hours after a high-fat meal) for l-amphetamine after administration of MYDAYIS 50 mg with high fat meal. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption and exposure to the intact capsule taken in the fasted state *[see Dosage and Administration (2.3)]*.

Effect of Alcohol

The *in vitro* testing showed increases in amphetamine release rate from MYDAYIS capsules in the presence of 20% and, more noticeably, 40% alcohol. There is no *in vivo* study conducted for the effect of alcohol on drug exposure.

Elimination

Metabolism

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 yet been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-aphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase. Amphetamines are not an *in vitro* inhibitor of the major human CYP450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), nor was

it an *in vitro* inducer of CYP1A2, CYP2B6 or CYP3A4/5. Amphetamines are not an *in vitro* substrate for P-gp.

Excretion

The renal excretion is the primary route for elimination of d- and l-amphetamine and its metabolites after administration of MYDAYIS.

At normal urine pHs, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30 to 40% of the dose is recoverable in urine as amphetamine itself. Urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination. Urinary recovery of amphetamine has been reported to range from 1% to 75%, and the fraction of a dose hepatically metabolized is dependent on urine pH. Consequently, both hepatic and renal dysfunctions have the potential to alter the elimination of amphetamine and could result in prolonged exposures *[see Drug Interactions (7.1)]*.

Specific Populations

Age

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of MYDAYIS in pediatric patients with ADHD 13 to 17 years old and healthy adult subjects (19 to 52 years) indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range.

PK data from patients age 13 to 17 years (n=14) who received a single 25 mg MYDAYIS capsule was scaled (based on PK proportionality) and compared with PK data from adult patients 19 to 51 years (n=20) who received 37.5 mg. Based on dose proportionality, a single-dose MYDAYIS capsule administered to pediatric patients age 13 to 17 years (n=14) would produce about 21% to 31% higher C_{max} for d- and l-amphetamine and 21% to 31% higher AUC for d- and l-amphetamine, compared to the same dose of MYDAYIS capsule administered to adults (age 19 to 51 years).

Male and Female Patients

In pharmacokinetic studies, systemic exposure to d- and l-amphetamine was similar in women (N=41) and in men (N=61).

Racial Groups

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Whites (N=41), Blacks (N=27), and Hispanics (N=34).

Patients with Renal impairment

The effect of renal impairment on d- and l-amphetamine after administration of MYDAYIS has not been studied.

In a pharmacokinetic study of lisdexamfetamine in adult subjects with normal and impaired renal function mean 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) patients. Dialysis did not significantly affect the clearance of d-amphetamine. The impact of renal impairment on the disposition of amphetamine would be expected to be similar between oral administration of lisdexamfetamine and MYDAYIS *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which d, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 3, 2, and 1 times, respectively, the maximum recommended human dose of 50 mg/day on a mg/m^2 body surface area basis in adults.

Mutagenesis

Amphetamine, in the enantiomer ratio present, d- to l- ratio of 3:1, was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility

Amphetamines, in the enantiomer ratio, d- to l- 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 (approximately 6 times the maximum recommended human dose of 25 mg/day given to adolescents on a mg/m^2 body surface area basis).

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

Efficacy of MYDAYIS in the treatment of ADHD was established in the following trials:

- Three short-term trials in adults (18 to 55 years, Studies 1, 2, and 3)
- Two short-term trials in pediatric patients (13 to 17 years, Studies 4 and 5)

Adult Patients (18 to 55 years) with ADHD

The approved adult doses, 12.5 mg, 25 mg, and 37.5 mg are based on Studies 1 and 3 and the 50 mg dose efficacy is based on Study 2. Doses up to 75 mg per day (1.5 times the maximum recommended adult dosage) were evaluated, but demonstrated no additional clinical benefit.

A 4 week, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study (Study 1) was conducted in adults aged 18 to 55 years (N=275) who met DSM-5 criteria for ADHD. Patients were randomized in a 1:1:1 ratio, to two MYDAYIS treatment groups and a placebo group. Group 1 received a dose of 12.5 mg/day throughout the study. Group 2 were titrated on a weekly basis from the initial dose 12.5 mg until target dose of 37.5 mg/day was reached by Week 3 and were maintained at 37.5 mg throughout the study. Group 3 received placebo.

The primary efficacy endpoint was defined as the change from baseline of the adult ADHD-Rating Scale (RS) with prompts total score at Week 4. Baseline adult ADHD-RS with prompts total score was defined as the last valid adult ADHD-RS with prompts total score assessment prior to taking the first dose of double-blind investigational product, usually at Visit 2. The primary comparison of interest was at Week 4 for each MYDAYIS dose compared with placebo. MYDAYIS demonstrated a statistically significant treatment effect compared with placebo on change of ADHD-RS total score from baseline at visit 6 (Week 4), for both 12.5 mg and 37.5 mg doses respectively (Study 1 in *Table 4*). Patients on MYDAYIS also showed statistically significantly greater improvement on the Clinical Global Impression of Improvement (CGI-I) score compared with placebo treatment.

Two multicenter, randomized, double-blind, placebo-controlled, crossover studies of MYDAYIS 25 mg/day (Study 3) and 50 mg/day (Study 2) were conducted in adult patients who met DSM-IV TR criteria for ADHD. The efficacy was determined using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. Efficacy assessments were conducted at 2, 4, 8, 12, 14, and 16 hours post-dose using the PERMP. MYDAYIS treatment, compared to placebo, reached statistical significance at either 2 hours (Study 2) or 4 hours (Study 3) post-dose to 16 hours post-dose in both studies. In a prespecified supplementary analysis for Study 2, the maximum approved dose of MYDAYIS (50 mg) demonstrated a statistically significant treatment effect compared with placebo beginning at 2 to 16 hours post-dose (Study 2 and Study 3 in *Table 4*).

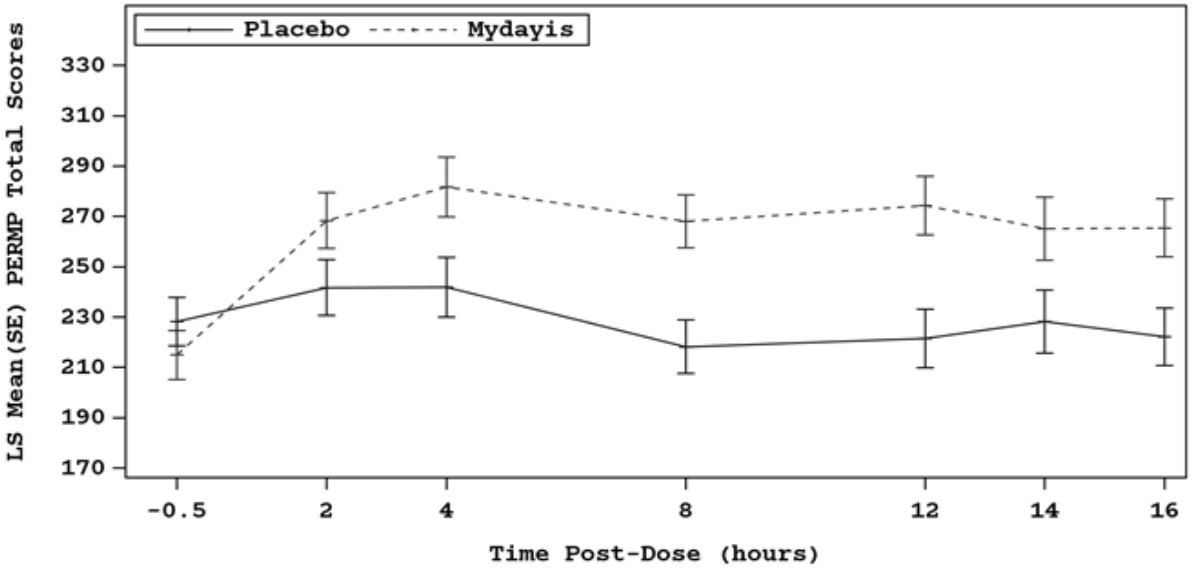
Pediatric Patients (13 to 17 years) with ADHD

A 4 week, randomized, double-blind, multicenter, placebo-controlled, dose-optimization, safety and efficacy study (Study 4) was conducted. In Study 4, the 157 pediatric patients 13 to 17 years old who met DSM-IV TR criteria for ADHD, were randomized in a 1:1 ratio to MYDAYIS or placebo group. Subjects were titrated from a dose of 12.5 mg/day until an optimal dose was reached (up to a maximum dose of 25 mg); this dose was maintained during the dose-maintenance period (Study 4 in *Table 4*).

The primary efficacy endpoint was defined as the change from baseline of the ADHD-RS-IV Total Score at Week 4. The baseline ADHD-RS-IV Total Score was defined as the last valid ADHD-RS-IV Total Score assessment prior to taking the first dose of double-blind investigational product, usually at Visit 2. MYDAYIS demonstrated a statistically significant treatment effect compared with placebo on the change of ADHD RS-IV total scores from baseline at Visit 6 (Week 4). MYDAYIS also showed statistically significantly greater improvement on the Clinical Global Impression of Improvement (CGI-I) score at Visit 6 (Week 4).

A multicenter, randomized, double-blind, placebo-controlled, crossover study of MYDAYIS 25 mg/day (Study 5) was conducted in adolescent patients who met DSM-IV TR criteria for ADHD. The efficacy was determined using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. Efficacy assessments were conducted at 2, 4, 8, 12, 14, and 16 hours post-dose using the PERMP. MYDAYIS treatment, compared to placebo, reached statistical significance at 2 to 16 hours post-dose (Study 5 in *Table 4*, *Figure 2*).

Figure 2: LS Mean (SE) PERMP Total Score by Treatment and Time-Point for Adolescents Ages 13 to 17 with ADHD After 1 Week of Double Blind Treatment (Study 5)



LS Mean: least-squares mean; SE: standard error

In both adults and pediatric patients, examination of a population subset based on gender or race did not reveal any differences.

Table 4: Summary of Primary Efficacy Results from Short-Term Studies of MYDAYIS in Adult and Pediatric Patients with ADHD

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference[a] (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	MYDAYIS (12.5 mg/day)* MYDAYIS (37.5 mg/day)* Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7, -4.4) -13.4 (-17.1, -9.7)
Study 2 (18 to 55 years)	Average PERMP	MYDAYIS (50 mg/day)* Placebo	239.2 (75.6)[b] 249.6 (76.7)[b]	293.23[c] 274.85[c]	18.38 (11.28, 25.47)
Study 3 (18 to 55 years)	Average PERMP	MYDAYIS (25 mg/day)* Placebo	217.5 (59.6)[b] 226.9 (61.7)[b]	267.96[c] 248.67[c]	19.29 (10.95, 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)[d]	ADHD-RS-IV	MYDAYIS (12.5-25 mg/day)* Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6, -4.8)
Study 5 (13 to 17 years)	Average PERMP	MYDAYIS (25 mg/day)* Placebo	214.5 (87.8)[b] 228.7 (101)[b]	272.67[c] 231.41[c]	41.26 (32.24, 50.29)

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

* Doses statistically significantly superior to placebo.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Pre-dose PERMP total score.

[c] LS Mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline.

[d] Results represent subgroup of Study 4 and not the total population.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

MYDAYIS extended-release capsules are available as:

- 12.5 mg: Green body/green cap (imprinted with black SHIRE 465 and 12.5 mg), bottles of 100, NDC 54092-468-01
- 25 mg: Ivory body/green cap (imprinted with black SHIRE 465 and 25 mg), bottles of 100, NDC 54092-471-01
- 37.5 mg: Ivory body/caramel cap (imprinted with black SHIRE 465 and 37.5 mg), bottles of 100, NDC 54092-474-01
- 50 mg: Ivory body/purple cap (imprinted with black SHIRE 465 and 50 mg), bottles of 100, NDC 54092-477-01

Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP.

Store at room temperature, 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of MYDAYIS, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), Overdosage (10)]*. Advise patients to store MYDAYIS in a safe place, preferably locked, and instruct patients to not give MYDAYIS to anyone else.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death with MYDAYIS use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate

Instruct patients that MYDAYIS can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects *[see Warnings and Precautions (5.3)]*.

Psychiatric Adverse Reactions

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

Long-Term Suppression of Growth in Pediatric Patients

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

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, Including Raynaud's Phenomenon]

Instruct patients beginning treatment with MYDAYIS about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking MYDAYIS. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Seizures

Caution patient that MYDAYIS may lower the convulsive threshold. Advise patients to contact their healthcare provider immediately and to discontinue MYDAYIS if a seizure occurs *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with concomitant use of MYDAYIS and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid *[see Contraindications (4), Warnings and Precautions (5.8), Drug Interactions (7.1)].* Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's syndrome may occur during treatment with MYDAYIS. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.10)].*

Concomitant Medications

Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions *[see Drug Interactions (7.1)]*.
Advise patient or caregiver of steps to take with MYDAYIS when a laboratory imaging procedure is ordered *[see Drug Interactions (7.2)].*

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to MYDAYIS during pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy

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

Lactation

Advise women not to breastfeed if they are taking MYDAYIS *[see Use in Specific Populations (8.2)]*.

Alcohol

Advise patients to avoid alcohol while taking MYDAYIS. Consumption of alcohol while taking MYDAYIS may result in a more rapid release of the dose of mixed amphetamine salts *[see Clinical Pharmacology (12.3)]*.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

For more information call 1-877-825-3327.

MYDAYIS is a registered trademark of Takeda Pharmaceuticals U.S.A., Inc.

DSM-IV-TR is a registered trademark of the American Psychiatric Association.

MYD365

MEDICATION GUIDE
MYDAYIS® (my-DAY-is)
(mixed salts of a single-entity amphetamine product)
extended-release capsules, CII

What is the most important information I should know about MYDAYIS?
MYDAYIS may cause serious side effects, including:

- **Abuse, misuse, and addiction.** MYDAYIS has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of MYDAYIS, other amphetamine containing medicines, and methylphenidate containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of MYDAYIS or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with MYDAYIS and will monitor you or your child during treatment.
  - MYDAYIS may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
  - Do not give MYDAYIS to anyone else. See "**What is MYDAYIS?"** for more information.
  - Keep MYDAYIS in a safe place and properly dispose of any unused medicine. See **"How should I store MYDAYIS?"** for more information.

  Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease. Your healthcare provider should check you or your child carefully for heart problems before starting MYDAYIS. Tell your healthcare provider if you or your child have any heart problems, heart disease, heart defects.

  Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with MYDAYIS.
- **Increased blood pressure and heart rate.** Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with MYDAYIS.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

  Tell your healthcare provider about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

  Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems while taking MYDAYIS, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is MYDAYIS?
MYDAYIS is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in people 13 years of age and older.

MYDAYIS is not for use in children 12 years of age and younger.

MYDAYIS is a federally controlled substance (CII) because it contains amphetamine that can be a target for people who abuse prescription medicines or street drugs. Keep MYDAYIS in a safe place to protect it from theft. Never give your MYDAYIS to anyone else, because it may cause death or harm them. Selling or giving away MYDAYIS may harm others and is against the law.

Who should not take MYDAYIS?
Do not take MYDAYIS if you or your child are:

- allergic to amphetamine or any of the ingredients in MYDAYIS. See the end of the Medication Guide for a complete list of ingredients in MYDAYIS.
- taking, or have stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue.

Before taking MYDAYIS, tell your healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects or high blood pressure, or have a family history of sudden death or heart problems
- have mental problems including psychosis, mania, bipolar illness or depression, or have a family history of suicide, bipolar illness, or depression

- have circulation problems in fingers and toes
- have or have had seizures
- have kidney problems
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if MYDAYIS will harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with MYDAYIS.
  - There is a pregnancy registry for females who are exposed to MYDAYIS during pregnancy. The purpose of the registry is to collect information about the health of females exposed to MYDAYIS and their baby. If you or your child becomes pregnant during treatment with MYDAYIS, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/research/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. MYDAYIS passes into breast milk. You should not breastfeed during treatment with MYDAYIS.

Tell your healthcare provider about all the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
MYDAYIS may affect the way other medicines work, and other medicines may affect how MYDAYIS works. Taking MYDAYIS with other medicines can cause serious side effects.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Know the medicines that you or your child take. Keep a list of your medicines with you to show your or your child's healthcare provider and pharmacist when you or your child get a new medicine.
Your healthcare provider will decide whether MYDAYIS can be taken with other medicines. **Do not start any new medicine during treatment with MYDAYIS without talking to your or your child's healthcare provider first.**

Your healthcare provider may tell you to stop taking MYDAYIS for a short time before you get certain imaging tests because MYDAYIS may impact the results of some tests.

How should I take MYDAYIS?

- Take MYDAYIS exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take MYDAYIS 1 time each day in the morning right after you wake-up. MYDAYIS may last up to 16 hours and can cause difficulty sleeping.
- If you miss a dose of MYDAYIS, **do not** take your dose later in the day or double your dose to make up for a missed dose. Take your MYDAYIS dose the next morning at your regularly scheduled time.
- MYDAYIS can be taken with or without food but take it the same way each time.
- Swallow MYDAYIS capsules whole **or** if MYDAYIS capsules cannot be swallowed whole, the capsules may be opened and sprinkled over a spoonful of applesauce.
  - swallow all of the applesauce and medicine mixture right away
  - **do not** chew the applesauce and medicine mixture
  - **do not** store the sprinkled applesauce
  - **do not** divide the medicine in the capsule. Take all the contents in the capsule.
- The dose (strength) of MYDAYIS is not the same as other amphetamine medicines. **Do not** change between MYDAYIS and other amphetamine medicines that have the same strength.

If you or your child take too much MYDAYIS, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid during treatment with MYDAYIS?
You should avoid drinking alcohol during treatment with MYDAYIS.

What are possible side effects of MYDAYIS?
MYDAYIS may cause serious side effects, including:

- See **"What is the most important information I should know about MYDAYIS?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with MYDAYIS. Your healthcare provider may stop your child's MYDAYIS treatment if they are not growing or gaining weight as expected.

- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon). Signs and symptoms may include:**
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you have or your child has any numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

  Call your healthcare provider if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with MYDAYIS.
- **Seizures.** Your healthcare provider will stop treatment with MYDAYIS if you have a seizure.
- **Serotonin syndrome.** This problem may happen when MYDAYIS is taken with certain other medicines and may be life-threatening. Call your healthcare provider or go to the nearest hospital emergency room if you get symptoms of serotonin syndrome which may include:
  - agitation, hallucinations, coma
  - loss of coordination
  - flushing
  - fast heartbeat
  - seizures
  - confusion
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - dizziness
  - changes in blood pressure
  - muscle stiffness or tightness
  - high body temperature (hyperthermia)
- **New or worsening tics or worsening Tourette's Syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with MYDAYIS.

The most common side effects of MYDAYIS include:

- trouble sleeping
- decreased appetite
- dry mouth
- increased heart rate
- anxiety
- nausea
- irritability
- weight loss

These are not all the possible side effects of MYDAYIS.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MYDAYIS?

- Store MYDAYIS at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect MYDAYIS from light.
- Store MYDAYIS in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired MYDAYIS by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix MYDAYIS with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away MYDAYIS in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep MYDAYIS and all medicines out of the reach of children.

General information about the safe and effective use of MYDAYIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MYDAYIS for a condition for which it was not prescribed. Do not give MYDAYIS to other people, even if they have the same condition. It may harm them and it is against the law. You can ask your pharmacist or healthcare provider for information about MYDAYIS that is written for health professionals.

What are the ingredients in MYDAYIS?

Active ingredients: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate

Inactive ingredients: hard gelatin capsules, ethylcellulose, hydroxypropyl methylcellulose, methacrylic acid copolymer, methyl acrylate, methyl methacrylate, Opadry® beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain gelatin, titanium dioxide, yellow iron oxide and edible inks. The 12.5 mg and 25 mg capsules also contain FD&C Blue #2. The 37.5 mg also contains red iron oxide. The 50 mg capsule also contains D&C Red #28, D&C Red #33, and FD&C Blue #1.

Distributed by:
Takeda Pharmaceuticals America, Inc., Cambridge, MA 02142

For more information about MYDAYIS go to www.mydayis.com or call 1-877-825-3327.