

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

<p>WARNING: ABUSE AND DEPENDENCE See full prescribing information for complete boxed warning.</p> <ul style="list-style-type: none"> • CNS stimulants, including MYDAYIS, other amphetamine - containing products, and methylphenidate, have a high potential for abuse and dependence (5.1, 9.3) • Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (9.2, 9.3)
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-----**WARNINGS AND PRECAUTIONS**-----

- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic. (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. (5.4)
- *Long-Term Suppression of Growth:* Monitor height and weight in pediatric patients during treatment. (5.5)
- *Peripheral Vasculopathy, including Raynaud’s phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Seizures:* May lower the convulsive threshold. If a seizure occurs, discontinue MYDAYIS. (5.7)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdose situations. If it occurs, discontinue MYDAYIS and initiate supportive treatment. (5.8)

-----**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 taken 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 overdose, 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)

-----**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 Shire US Inc. 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 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)
- *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.

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FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE AND DEPENDENCE

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Information Prior to Initiating Treatment
- 2.2 General Instructions for Use
- 2.3 Dosing Information
- 2.4 Maintenance Treatment
- 2.5 Dosage Modifications due to Drug Interactions
- 2.6 Dosage in Patients with Renal Impairment
- 2.7 Switching from other Amphetamine Products

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Long-Term Suppression of Growth
- 5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
- 5.7 Seizures
- 5.8 Serotonin Syndrome
- 5.9 Potential for Overdose Due to Medication Errors

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Adverse Reactions Associated with the Use of Amphetamines

7 DRUG INTERACTIONS

- 7.1 Drugs Having Clinically Important Interactions with Amphetamines
- 7.2 Drug/Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

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

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 Important Information Prior to Initiating Treatment

Prior to initiating treatment with MYDAYIS, assess for the presence of cardiac disease (e.g., a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) [see *Warnings and Precautions (5.2)*].

Assess the risk of abuse, prior to prescribing and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for MYDAYIS use [see *Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9)*].

2.2 General Instructions for Use

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)*].

Pharmacological treatment of ADHD may be needed for an extended period. Periodically re-evaluate the long-term use of MYDAYIS and adjust dosage as needed.

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 Dosing Information

Adult Use (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 Use (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 m²), 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 m²). 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 following discontinuation of treatment with a monoamine oxidase inhibitor, because of an increased risk of hypertensive crisis [see *Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

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

5.2 Serious Cardiovascular Reactions

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

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension [*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 mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms

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

5.5 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including MYDAYIS. 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)*].

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 [*Use in Specific Populations (8.4)*].

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

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, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation

for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

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 co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to MYDAYIS. 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 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) and Overdosage (10)*].

6 ADVERSE REACTIONS

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

- Drug Dependence [see *Boxed Warning, Warnings and Precautions (5.1), and 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) and Drug Interactions (7.1)*]
- Serious Cardiovascular Reactions [see *Warnings and Precautions (5.2)*]
- Blood Pressure and Heart Rate Increases [see *Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [see *Warnings and Precautions (5.4)*]
- Long-Term Suppression of Growth [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)*]

6.1 Clinical Trial Experience

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

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 $\geq 2\%$ 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 $\geq 2\%$ 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 ¹	4%	2%
	Erectile Dysfunction ²	2%	1%

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

¹ Dysmenorrhea was observed in 11 females

² 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 $\geq 2\%$ compared to placebo.

Table 2 Adverse Reactions Reported by $\geq 2\%$ 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 post approval 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.

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).

Eye Disorders: Mydriasis.

Gastrointestinal: Unpleasant taste, constipation.

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

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

Skin: Alopecia.

Vascular Disorders: Raynaud's phenomenon.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 3 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 MYDAYIS during or within 14 days following the administration of MAOI [see <i>Contraindications (4)</i>].
Examples	selegiline, isocarboxazid, phenelzine, tranylcypromine
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 <i>Warnings and Precautions 5.7</i>].
Examples	Selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
Alkalinizing Agents	
Clinical Impact	May increase exposure to amphetamine and exacerbate the action of amphetamine.
Intervention	Caution should be taken when co-administering MYDAYIS and gastrointestinal and urinary alkalinizing agents.
Examples	Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate; proton pump inhibitors [e.g. omeprazole]) Urinary alkalinizing agents (e.g. acetazolamide, some thiazides)
Acidifying Agents	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose of MYDAYIS based on clinical response.

Examples	Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid) Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)
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.
Examples	desipramine, protriptyline
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.
Examples	paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir.
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.
Examples	omeprazole, esomeprazole, pantoprazole, cimetidine

7.2 Drug/Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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/m² body surface area basis. However, in a pre- and post-natal 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 2-4% and 15-20%, 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/m² 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/m² 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/m² 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

Safety and effectiveness 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)*].

Safety and effectiveness have not been established in pediatric patients ages 12 years and younger.

In clinical trials, pediatric patients 6 to 12 years of age experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including higher rates of insomnia (30% versus 8%) and appetite decreased (43% versus 22%). In addition, amphetamine systemic exposures (both *d*- and *l*-) in patients 6 to 12 years of age following a

single dose were higher than those observed in adults at the same dose (72-79% higher C_{max} and approximately 83% higher AUC).

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 7-13 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. Post-dosing 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, which are in Schedule II.

9.2 Abuse

MYDAYIS is a CNS stimulant that contains mixed amphetamine salts which have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

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

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

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a specific dose of a drug results in a reduction of the drug's desired and/or undesired effects over time, in such a way that a higher dose of the drug is required to produce the same effect that was once obtained at a lower dose) may occur during the chronic therapy of CNS stimulants including MYDAYIS.

Dependence

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

10 OVERDOSAGE

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

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

The prolonged release of mixed amphetamine salts from MYDAYIS should be considered when treating patients with overdose.

D-amphetamine is not dialyzable.

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.

<u>EACH CAPSULE CONTAINS:</u>	<u>CAPSULE STRENGTHS</u>			
	<u>12.5 mg</u>	<u>25 mg</u>	<u>37.5 mg</u>	<u>50 mg</u>
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.

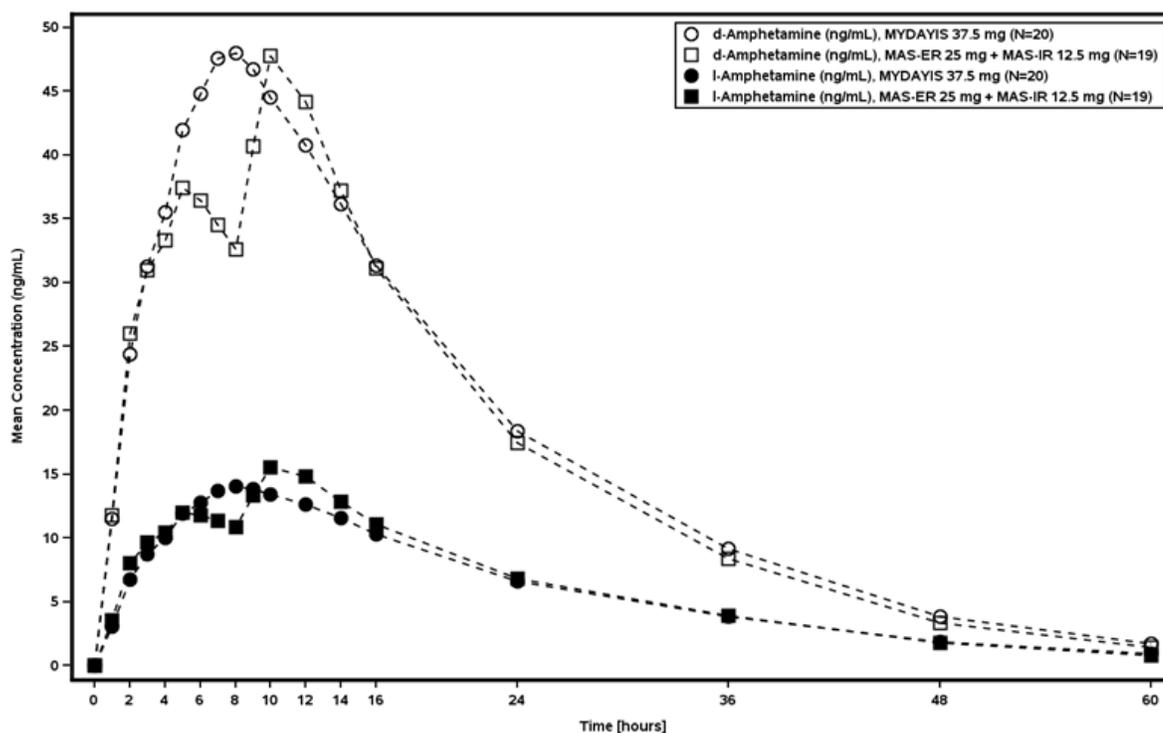
12.3 Pharmacokinetics

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 – 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 – 11 hours and *l*-amphetamine from 10 – 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 *Dosing 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-amphetamine. 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%-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 21-31% higher C_{max} for *d*- and *l*-amphetamine and 21-31% 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 white (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 m²) 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/m² 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/m² 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, multi-center, 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 multi-center, 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 pre-specified 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).

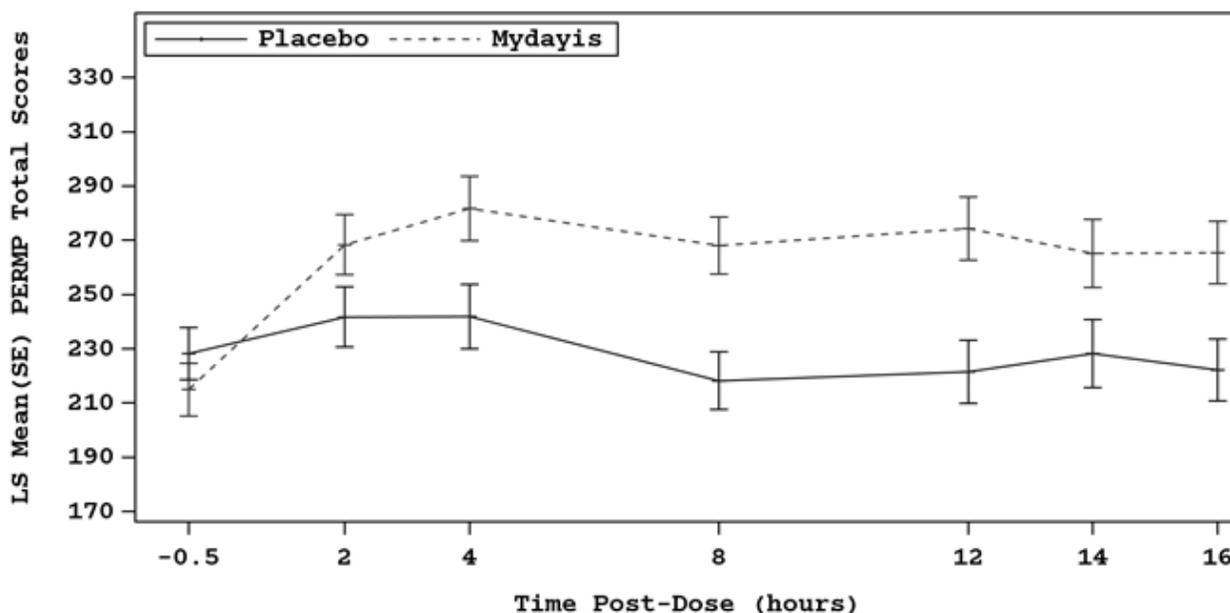
Pediatric patients (13 to 17 years) with ADHD

A 4-week, randomized, double-blind, multi-center, 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 multi-center, 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 (18-55 years)	ADHD-RS	MYDAYIS (12.5 mg/day)*	39.8 (6.38)	-18.5	-8.1 (-11.7, -4.4)
		MYDAYIS (37.5 mg/day)*	39.9 (7.07)	-23.8	-13.4 (-17.1, -9.7)
		Placebo	40.5 (6.52)	-10.4	
Study 2 (18-55 years)	Average PERMP	MYDAYIS (50mg/day)*	239.2 (75.6) ^b	293.23 ^c	18.38 (11.28, 25.47)
		Placebo	249.6 (76.7) ^b	274.85 ^c	
Study 3 (18-55 years)	Average PERMP	MYDAYIS (25 mg/day)*	217.5 (59.6) ^b	267.96 ^c	19.29 (10.95, 27.63)
		Placebo	226.9 (61.7) ^b	248.67 ^c	
Pediatric Studies					
Study 4 (13-17 years) ^d	ADHD-RS-IV	MYDAYIS (12.5-25 mg/day)*	36.7 (6.15)	-20.3	-8.7 (-12.6, -4.8)
		Placebo	38.3 (6.67)	-11.6	
Study 5 (13-17 years)	Average PERMP	MYDAYIS (25 mg/day)*	214.5 (87.8) ^b	272.67 ^c	41.26 (32.24, 50.29)
		Placebo	228.7 (101) ^b	231.41 ^c	

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

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.

* Doses statistically significantly superior to placebo.

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

Disposal

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

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired MYDAYIS at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix MYDAYIS with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard MYDAYIS in the household trash.

17 PATIENT COUNSELING INFORMATION

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

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients and their caregivers that MYDAYIS is a federally controlled substance because it can be abused or lead to dependence. Advise patients to store MYDAYIS in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired MYDAYIS by a medicine take-back program if available [*see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9)*].

Serious Cardiovascular Risks

Advise patients, caregivers, and family members that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with 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)*].

Blood Pressure and Heart Rate Increases

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 Risks

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

Advise patients, family members, and caregivers that amphetamines 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) 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)*].

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)*].

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421

Made in USA

For more information call 1-800-828-2088

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MEDICATION GUIDE
MYDAYIS (*my-DA Y-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 can cause serious side effects, including:

- **Abuse and dependence.** MYDAYIS, other amphetamine containing medicines, and methylphenidate have a high chance for abuse and can cause physical and psychological dependence. Your healthcare provider should check you or your child for signs of abuse and dependence before and during treatment with MYDAYIS.
- Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.

- **Heart-related problems, including:**

- sudden death, stroke, and heart attack in adults
- sudden death in people who have heart problems or heart defects
- increased blood pressure and heart rate

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 defects, high blood pressure, or a family history of these problems.

Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with MYDAYIS.

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

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- **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 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.

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 taken within the past 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI).

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

- have heart problems, heart defects or high blood pressure
- have mental problems including psychosis, mania, bipolar illness or depression, or have a family history of suicide
- have circulation problems in fingers and toes

- have or have had seizures
- have kidney problems. You should not take MYDAYIS if you have end stage renal disease (ESRD).
- 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 during treatment with MYDAYIS.
- 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 takes, 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 medicines used to treat depression including MAOIs.

Know the medicines that you or your child takes. 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.**

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.
- MYDAYIS capsules may be swallowed 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
- Your healthcare provider may sometimes stop MYDAYIS treatment for a while to check ADHD symptoms.
- **If you or your child takes too much MYDAYIS, call your healthcare provider 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 can 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, or other changes in mental status
 - problems controlling your movements or muscle twitching
 - fast heartbeat
 - sweating or fever
 - nausea, vomiting, or diarrhea
 - muscle stiffness or tightness

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 authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or 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.

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 healthcare provider or pharmacist for information about MYDAYIS that was written for healthcare 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.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

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For more information about MYDAYIS go to www.mydayis.com or call 1-800-828-2088.