AJMC®
Managed Markets Network®

Mydayis® CII

(mixed salts of a single-entity amphetamine product)

12.5 | 25 | 37.5 | 50 mg extended-release capsules

CLINICAL MONOGRAPH

INDICATION AND LIMITATIONS OF USE

MYDAYIS® is indicated for the treatment of ADHD in patients ≥13 years. Patients ≤12 years experienced higher plasma exposure at the same dose and higher rates of adverse reactions, mainly insomnia and decreased appetite.

IMPORTANT SAFETY 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.**

Please see additional Important Safety Information on pages 2 and 3, and accompanying Full Prescribing Information located after page 18.

IMPORTANT SAFETY INFORMATION (continued)

• Contraindications

- Known hypersensitivity to amphetamines or other ingredients of Mydayis. Angioedema and anaphylactic reactions have been reported with other amphetamines.
- Use with monoamine oxidase inhibitors (MAOIs) or within 14 days of last MAOI dose, due to increased risk of hypertensive crisis.

• Warnings and Precautions

- Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulants at recommended doses, as well as sudden death in pediatric patients with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Mydayis treatment.
- CNS stimulants cause increased blood pressure (mean increase ~2-4 mm Hg) and heart rate (mean increase ~3-6 bpm). Monitor for tachycardia and hypertension.
- *Exacerbation of Pre-existing Psychosis*: 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*: May induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen 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*: At recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients with no prior history of psychotic illness or mania. Discontinue if symptoms occur.

Warnings and Precautions (continued)

- CNS stimulants are associated with weight loss and slowing of growth rate in pediatric patients (monitor weight and height). Treatment may need to be interrupted in patients not growing or gaining weight as expected. Mydayis is not approved in pediatric patients ≤12 years.
- CNS stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; very rare sequelae include digital ulceration and/or soft tissue breakdown. Careful observation for digital changes is necessary during treatment with ADHD stimulants; further evaluation and referral may be required.
- Mydayis may lower the convulsive threshold in patients with prior history of seizure, prior EEG abnormalities in the absence of seizures, and in patients without a history of seizures and no prior EEG evidence of seizures. Discontinue if a seizure occurs.
- Increased risk of serotonin syndrome when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. Discontinue Mydayis if it occurs and initiate supportive treatment.
- To avoid substitution errors and overdosage, do not substitute for other amphetamines on a mg-per-mg basis because of different amphetamine base compositions and differing PK profiles.

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.
- *Adults*: insomnia, decreased appetite, decreased weight, dry mouth, increased heart rate, and anxiety.

Pregnancy and Lactation

Mydayis may cause fetal harm. Breastfeeding is not recommended during Mydayis treatment.

Please see accompanying Full Prescribing Information located after page 18.

AJMC® Monograph

A CLINICAL INTRODUCTION TO MYDAYIS

(MIXED SALTS OF A SINGLE-ENTITY AMPHETAMINE PRODUCT)

Table of Contents

DEFINITION OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that emerges before the age of 12 years. Affected individuals may have symptoms of inattention and/or hyperactivity/impulsivity that are not better explained by another medical condition.[1]

Clinicians apply a specific set of diagnostic criteria when diagnosing ADHD, as established by the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*® (*DSM-5*). Some patients have symptoms of inattention, such as failure to notice details, difficulty with organization, or easy distraction by external stimuli. Other patients show symptoms of impulsivity/hyperactivity, such as excess fidgeting, difficulty waiting, or interrupting. Some patients experience symptoms from both the inattention and impulsivity/hyperactivity diagnositc criteria. A full list of symptoms can be found in *DSM-5*.[1]

For diagnosis, these symptoms must have existed for at least 6 months. Children without ADHD may also show impulsivity and inattention, but in children with ADHD, the severity of symptoms cannot be explained by normal cognitive development. Moreover, these symptoms must interfere with the patient's academic, social, or occupational functioning. Individuals must have these symptoms in at least 2 different settings.[1]

INCIDENCE AND PREVALENCE OF ADHD

Some children diagnosed with ADHD grow out of the disorder, but many do not. About 70% of children diagnosed with ADHD will continue to experience symptoms as adolescents. More than half of patients diagnosed with ADHD as children continue to have symptoms into adulthood.[2]

The incidence of ADHD is somewhat unclear. The *DSM-5* describes the condition as occurring in about 5% of children and in 2.5% of adults.[1] However, a 2011-2012 study led by the CDC found that 11% of children aged 4-17 years had received an ADHD diagnosis, totaling 6.4 million children in the United States.[3] The same study found that 69% of children in this age group currently diagnosed with ADHD were taking some sort of medication for the condition.[3]

More males than females receive a diagnosis of ADHD, at a ratio of about 2 to 1 in children.[1] Patients from all ethnic backgrounds can present with symptoms of ADHD. The exact cause of ADHD is unknown.[2]

CLINICAL AND ECONOMIC IMPACT OF ADHD AND ASSOCIATED CONDITIONS

ADHD symptoms can negatively impact social and academic/occupational functioning. People with ADHD also may have comorbid psychiatric conditions, which add to the overall impact of the disorder. The diagnosing physician should conduct a full differential diagnosis and assess for comorbid conditions.[1]

Additionally, ADHD significantly impacts the US economy. Estimates of the costs resulting from ADHD range from $143 billion to $266 billion annually. These include healthcare costs, income losses and reductions in economic productivity, educational expenditures, and costs from the US justice system.[7] Even using the lower cost estimate, this represents a substantial economic burden.

Of these costs, $105 billion to $194 billion annually result from adults with ADHD or adult family members of patients with ADHD. In adults, the greatest costs are due to productivity and income losses, with estimates from $87 billion to $138 billion annually.[7] Estimates of productivity losses for adults with ADHD range from roughly $200 to $6700 annually per person for 18- to 64-year-old employees.[7] Additionally, annual household income is lowered by roughly $10,000 to $12,000 in adults with ADHD.[7]

The largest cost components for children are healthcare ($21 billion to $44 billion) and costs from the educational sector ($15 billion to $25 billion).[7] One study estimated the ADHD-related incremental costs of education in 3- to 4-year-olds at roughly $12,000 per year per student.[7] Two studies estimated annual incremental educational costs for 5- to 18-year olds at $2200 to $4700 annually.[7]

POSSIBLE CAUSES OF ADHD

ADHD is a neurodevelopmental disorder thought to involve many areas of the brain; its etiology is not fully understood, and further research is needed to understand its exact cause. However, there are theories that support a neurobiological basis of ADHD, as well as influencing factors such as genetics and environmental.[2,8] Differences in biochemical brain activity are thought to play a role in the disease symptoms, including alterations in the availability of the neurotransmitters norepinephrine and dopamine. Norepinephrine may play more of a role in problem solving, planning, and remembering tasks. Dopamine may play a more important role in helping individuals maintain attention.[2]

Though ADHD is thought to affect several areas of the brain, the prefrontal cortex seems to be particularly significant. This region (dorsolateral, ventromedial, and right inferior) of the brain is associated with ADHD symptoms of inattention and distraction, the regulation of emotional responses, and behavior and judgment, all of which may be impaired in people with ADHD. Also, the prefrontal cortex has reciprocal connections with many brain regions that may have decreased activation or reduced size in people with ADHD.[8]

Additionally, researchers are beginning to learn more about the genetic factors that play a role in ADHD. Researchers estimate heritability of the disease is about 70% to 80%, and parents and siblings of children with ADHD have a 2- to 8-fold increased risk of having the condition.[9] However, environmental contributors may also play a lesser role. These might include such factors as prenatal substances exposures, nutrition, and other lifestyle and psychosocial factors.[10]

Central nervous system (CNS) psychostimulants are a first-line treatment option for ADHD.[11] Though their mechanism of action is not completely understood, researchers theorize that these stimulants work by increasing the concentrations of catecholamines (including dopamine and norepinephrine) in the prefrontal cortex.[11] Due to differences in release profiles, these drugs vary greatly in their pharmacokinetic and pharmacodynamic properties.[2] Because of this, products display variability in the timing of peak concentrations and the duration of therapeutic effect.[2]

MANAGEMENT OPTIONS IN ADHD

Some patients find nonpharmacological treatments helpful in the treatment of ADHD. These may include behavior management strategies, school interventions, and cognitive behavioral therapy. Pharmacological options are more commonly used, but some prescribers opt for combined therapy.[8]

Stimulant options for ADHD include methylphenidate, dexmethylphenidate, and amphetamine derivatives such as mixed amphetamine salts, lisdexamfetamine dimesylate, and dextroamphetamine. In general, stimulants are effective in about 70% of patients with ADHD. In clinical studies, these medications have demonstrated improvement in ADHD symptoms.[11]

A commonly perscribed first-line treatment for ADHD is methylphenidate, which is thought to work on dopamine and norepinephrine transporters to increase the availability of these neurotransmitters in the prefrontal cortex and other brain areas.[2] Amphetamine drugs are thought to have a similar mechanism to methylphenidate, while also increasing the release of dopamine.[2]

These medications are available in immediate-release, intermediate-acting, or long-acting formulations, each with different pharmacodynamic properties. In certain formulations, part of the medication is released immediately, and the remaining dose is released over a delayed period of time. Among products, there is variability in the timing of peak concentrations and the duration of the therapeutic effect. These various CNS stimulant medications are available as capsules, chewable tablets, liquid formulation, and in patch form.[2]

Nonstimulant medications for ADHD may be considered in individuals who do not respond to stimulants or have a contraindication to their use. Atomoxetine is thought to selectively inhibit the reuptake of norepinephrine, thereby increasing the concentrations of both norepinephrine and dopamine, but in a localized region of the brain.[2] Extended-release formulations of guanfacine and clonadine are alpha$_2$-agonist drugs which are thought to work in ADHD by mimicking the effects of norepinephrine at alpha$_2$ adrenoceptors in the prefrontal cortex.[2]

STIMULANT FORMULATIONS

Methylphenidate is available in short-acting preparations (lasting 2-5 hours), in intermediate formulations (lasting 6-8 hours), and long-acting formulations (lasting 9-12 hours). Similarly, amphetamine preparations are available in short-acting forms (lasting 4-6 hours) and in long-acting forms (lasting 8-12 hours).[2]

Researchers point out that time after school could be as important as time during school for developing social and academic skills. A variety of different mechanisms are available to provide delivery of long-acting stimulants for the treatment of ADHD. These include wax-matrix–based technology, osmotic oral release systems, prodrug delivery systems, and capsules containing beads with different drug release profiles. These systems can be used to design ADHD drugs with several different release profiles.[12]

Long-acting methylphenidate products have demonstrated efficacy for 9-12 hours, and long-acting amphetamine products have shown a similar duration of effect.[2] Yet even with these longer-acting formulations, adolescents and adults may need additional ADHD coverage during the day, and health care providers may opt to prescribe a second dose of an immediate-release short-acting product for some patients.[15]

INTRODUCING MYDAYIS

(MIXED SALTS OF SINGLE-ENTITY AMPHETAMINE PRODUCT)

Mydayis® is a product containing mixed salts of a single-entity amphetamine in extended-release capsules for oral use.[15] The FDA approved Mydayis in June 2017 for patients with ADHD aged 13 years and older. Safety and effectiveness have not been established in pediatric patients ages 12 years and younger. Patients under age 13 years experienced higher plasma levels of the medication at the same dose with corresponding higher rates of AEs, mostly insomnia and reduced appetite.[15]

It is important to note that Mydayis has a Boxed WARNING regarding abuse and dependence. **Specifically, CNS stimulants, including Mydayis, other amphetamine-containing produts, and methylphenidate, have a high potential for abuse and dependence. Healthcare providers should assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.**

Health care professionals play an important role in educating patients and family members about ADHD and its management options, including Mydayis. Because of this, it is important that providers be aware of the drug's mechanism of delivery, its proper dosage, and its efficacy and safety information. Providers should also be aware of drug interactions and concerns in special populations. Because Mydayis and other CNS stimulants are Schedule II drugs, providers must also educate patients about the appropriate use of such substances.[15]

The active ingredients of Mydayis are 4 amphetamine salts contained in equal amounts by weight: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate. The mixture includes a 3-to-1 ratio of dextro- (*d*-) to levo- (*l*-) amphetamine.[15]

The inactive ingredients of Mydayis 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 4 strengths include 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, and the 50-mg strength capsule has D&C Red #28, D&C Red #33,and FD&C Blue #1.[15]

DOSAGE AND ADMINISTRATION

Mydayis is available in extended-release capsules of 4 different strengths: 12.5 mg, 25 mg, 37.5 mg, and 50 mg (Table 1).[15]

Starting at a dose of 12.5 mg once daily in the morning, clinicians may titrate the dose upward in 12.5 mg increments. Clinicians should increase the dose no sooner than weekly to a maximum dose of 25 mg in pediatric patients (13 to 17 years old) and 50 mg in adult patients, based on therapeutic needs and response of the patient (Table 2).[15] Mydayis shows linear dose proportionality over the range of 12.5 mg to 50 mg. Doses above 50 mg/day in

TABLE 1. Mydayis Dosage and Appearance[15]

Extended-release capsules	Color	Imprint	Total amphetamine base equivalence
12.5 mg	Green body/green cap	SHIRE 465; 12.5 mg	7.8 mg
25 mg	Ivory body/green cap	SHIRE 465; 25 mg	15.6 mg
37.5 mg	Ivory body/light caramel cap	SHIRE 465; 37.5 mg	23.5 mg
50 mg	Ivory body/purple cap	SHIRE 465; 50 mg	31.3 mg

Each capsule contains equal parts by weight of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate.

TABLE 2. Dosing and Titration Information[15]

	Initial recommended starting dose	Dose adjustments	Maximum dose
Adults	12.5 mg once daily (25 mg acceptable for some adult patients)	12.5 mg increments, no sooner than weekly	50 mg daily (based on therapeutic needs and patient response)
Pediatrics (ages 13-17 years)	12.5 mg once daily	12.5 mg increments, no sooner than weekly	25 mg daily (individualized based on needs and patient response)

adults have shown no additional clinically meaningful benefit. It is also important to note that doses higher than 25 mg/day have not been evaluated in clinical trials in pediatric patients (13-17 years). Pharmacological treatment of ADHD may be needed for an extended period. As such, clinicians should periodically re-evaluate the long-term use of Mydayis and adjust the dosage, as needed.[15]

Mydayis should be taken orally. It can be taken with or without food, but should be taken the same way each time. Clinicians should recommend that their patients take it consistently either with or without food. Patients may swallow the capsule whole. Alternatively, patients can opt to open the capsule and sprinkle the entire contents on a spoonful of applesauce. Patients must swallow the entire mixture right away without chewing or storing. The dose of a single capsule should not be divided.[15]

Patients should take Mydayis once daily upon awakening. This is important due to the potential for insomnia and because effects may last up to 16 hours post-dose. If a dose is missed, patients should not take it later in the day and should not take additional medication to make up for the missed dose.[15]

Dosing Safety Information

Prior to treatment, providers should assess for cardiac disease and risk of abuse. After prescribing, it is important to keep careful prescription records, educate patients about abuse, monitor for signs of abuse, dependence and overdose, and periodically re-evaluate the need for Mydayis use.

Changes in dosing apply to specific populations. The adult starting dose is 12.5 mg/day in patients with severe renal impairment (max dose is 25 mg/day). In pediatric patients (13-17 years) with severe renal disease, the maximum dose is 12.5 mg/day, if tolerated. Mydayis is not recommended for use in patients with end-stage renal disease (ESRD).

To help avoid substitution errors and overdosage, clinicians should not substitute Mydayis for other amphetamine products on a milligram-for-milligram basis because of different amphetamine base compositions and differing pharmacokinetic profiles.

Metabolism

Although the enzymes involved in amphetamine metabolism have not yet been clearly defined, the liver enzyme CYP2D6 is known to be involved. Since this enzyme is genetically polymorphic, it may cause variations in amphetamine metabolism in the population.[15]

Excretion

Both *d*- and *l*-amphetamine and their metabolites are primarily

TABLE 3. Mydayis Pharmacokinetics[15]

	Peak plasma concentrations	Mean plasma elimination half-life of d-amphetamine	Mean plasma elimination half-life of l-amphetamine	Steady state achieved
Adults	8 hours	10-11 hours	10-13 hours	Day 7-Day 8
Pediatrics (aged 13 to 17 years)	7-10 hours	10-11 hours	10-13 hours	Day 7-Day 8

eliminated through the kidneys after administration of Mydayis. The amount of drug eliminated is highly dependent on pH and urine flow rates, with acidic pH and high flow rates resulting in increased renal elimination. The fraction of amphetamines metabolized by the liver is dependent on urine pH as well. Because of this, both hepatic and renal dysfunction may alter the elimination of amphetamine, and thus might cause prolonged drug exposure.[15]

Pharmacokinetics Across Gender, Race, and Age

Pharmacokinetic studies have shown that Mydayis exposure is similar in women (n = 41) and men (n = 61). Though formal pharmacokinetic studies across racial and ethnic groups have not been performed, exposure appears to be similar in Whites (n = 41), Blacks (n = 27), and Hispanics (n = 34). The pharmacokinetics of Mydayis vary by age (13-52 years), but differences in body weight appear to be the main cause of these differences.[15]

Clinical studies of Mydayis did not include sufficient numbers of subjects ages 65 and over to determine whether they respond differently from younger subjects. When starting a new drug for an elderly patient, one should generally start at the low end of the dosing range. These patients are more likely to have decreased hepatic, renal, or cardiac function, or other diseases or drug therapy that might impact drug metabolism and effect.[15]

The safety and effectiveness of Mydayis in patients with ADHD ages 13 to 17 have been established in two placebo-controlled studies. Safety and effectiveness have not been established in pediatric patients ages 12 years and younger. In clinical studies, patients ages 6 to 12 years experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including insomnia and decreased appetite.[15]

Pharmacokinetic Changes With Food and Alcohol

A high-fat meal does not affect the extent of absorption of *d*- and *l*-amphetamine when taken with Mydayis. However, a high-fat meal prolongs the Tmax by 5 hours for d-amphetamine (from 7.0 hours to 12.0 hours), and it prolongs the Tmax of l-amphetamine by 4.5 hours (from 7.5 hours to 12 hours) (Table 3).[15] Because of that, patients are advised to take Mydayis consistently either with or without food. In vitro studies showed that alcohol may increase the release rate of amphetamines. Because of this, clinicians should advise patients taking Mydayis to avoid using alcohol.[15]

Storage and Handling Instructions

Mydayis should be stored at room temperature in a tightly closed, light-resistant container. Temperature excursions permitted between 59°F and 86°F.[15]

Proper Disposal of CNS Stimulants

- Patients and clinicians should comply with local laws and regulations on the drug disposal of CNS stimulants. Because of the potential for abuse, remaining, unused, or expired Mydayis should be disposed of at authorized collection sites. Available sites may include law-enforcement locations or retail, hospital, or clinic pharmacies.

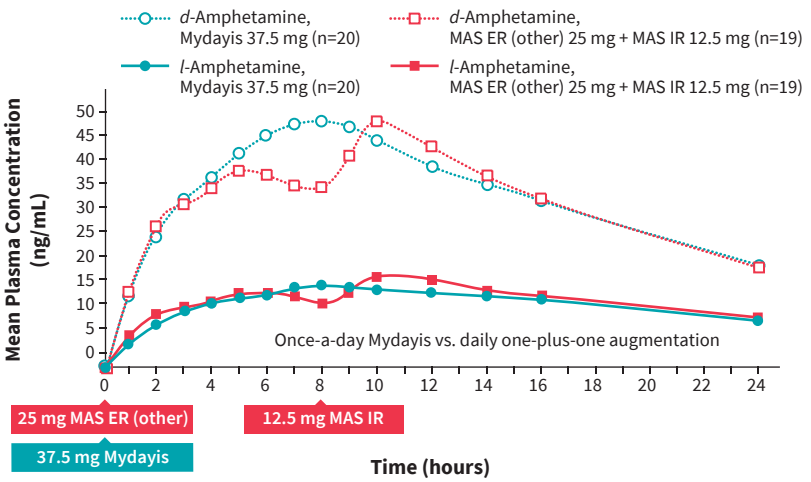
- If no authorized collector is available, mix Mydayis with an undesirable, nontoxic substance. Place mixture in a sealed plastic bag and discard in the household trash.[15]

Dosage Considerations With Tolerance and Dependence

Patients ≥13 years of age with ADHD may need to take Mydayis over an extended period of time. Clinicians should periodically evaluate the long-term use of the product and adjust dosage as needed.[15] It is also important for clinicians to understand that CNS stimulants like Mydayis can induce drug tolerance. Patients receiving chronic therapy with Mydayis may eventually require higher dosages to maintain the same therapeutic effect.[15]

Similarly, clinicians should be aware of the potential for drug dependence. A patient who abruptly stops taking a drug may experience symptoms such as extreme fatigue and depression. Clinicians should remember this possibility if a patient's dose is to be reduced and should consider tapering the drug.[15]

FIGURE 2. Mean Plasma Concentrations of *d*- and *l*-amphetamine Following Oral Administration of Mydayis[15,a]



Efficacy conclusions cannot be drawn from pharmacokinetic data. Mydayis contains d- and l-amphetamine in the ratio of 3:1.

[a]37.5 mg versus MAS-ER 25 mg followed by immediate-release MAS-IR 12.5 mg 8 hours later in adults.

Drug Interactions and Dosage

Agents that affect gastrointestinal and urinary pH can alter blood levels when taking Mydayis. Patients taking such agents may need corresponding dosage adjustment. Acidifying agents decrease blood levels of Mydayis, and alkalinizing agents increase blood levels. This includes gastrointestinal alkalinizing or acidifying agents, as well as urinary alkalinizing or acidifying agents.[15]

Gastric pH modulator drugs such as omeprazole may also cause changes in pharmacokinetic profile and drug exposure. These patients should be monitored for changes in drug response. CYP2D6 inhibitor drugs such as paroxetine and ritonavir may also increase exposure of amphetamine, so patients on these drugs may need a lower dose of Mydayis. Tricyclic antidepressants may also cause sustained increases of *d*-amphetamine in the brain, so these patients may need an adjusted dosage. Patients taking serotonergic drugs should also be started on lower doses of Mydayis and monitored carefully for signs of serotonin syndrome (**Table 4**).[15]

Because of the risks for interactions, patients should be advised to discuss any new prescriptions or over-the-counter medications with a health care provider.[15]

CONTRAINDICATIONS

Mydayis is contraindicated in patients with known hypersensitivity to amphetamines or other ingredients in Mydayis. Angioedema and anaphylactic reactions have been reported with other amphetamines. Due to the risk of increased risk of hypertensive crisis, Mydayis is also contraindicated in patients taking monoamine oxidase (MAO) inhibitors, or within 14 days of the last MAO inhibitor dose.[15]

MECHANISM OF ACTION, DELIVERY, AND RELEASE CHARACTERISTICS

Scientists do not understand the exact mechanisms of action of CNS stimulant drugs like amphetamines in ADHD therapy. However, it is known that amphetamines block the reuptake of norepinephrine and dopamine into presynaptic neurons. They also increase norepinephrine and dopamine release into the extraneuronal space (ie, space outside the neurons).[15]

TABLE 4. Drugs That Clinically Interact With Amphetamines[15]

MAOI Inhibitors	
Clinical impact	Monoamine oxidase inhibitor (MAOI) antidepressants slow amphetamine metabolism, increasing amphetamine's 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 an MAOI
Examples	Selegiline, isocarboxazid, phenelzine, tranylcypromine
Serotonergic Drugs	
Clinical impact	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)
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), 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 (eg, sodium bicarbonate; proton pump inhibitors [eg, omeprazole]); urinary alkalinizing agents (eg, 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 (eg, guanethidine, reserpine, glutamic acid HCl, ascorbic acid); urinary acidifying agents (eg, 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 pharmacokinetic 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

TABLE 5. Summary of Primary Efficacy Results From Short-Term Studies of Mydayis in Adult and Pediatric (13-17 years) Patients With ADHD[15]

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* 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 (18-55 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 (18-55 years)	Average PERMP	Mydayis 25 mg/ day* Placebo	217.5 (56.6)[b] 226.9 (61.7)[b]	267.96[c] 248.67[c]	19.29 (10.95, 27.63)
Pediatric Studies					
Study 4 (13-17 years)[d]	ADHD-RS-IV	Mydayis 12.5 mg/day to 25 mg/day* Placebo	36.7 (6.15) 38.3 (6.67)	–20.3 –11.6	–8.7 (–12.6, –4.8)
Study 5 (13-17 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)

ADHD indicates attention-deficit/hyperactivity disorder; ADHD RS IV, ADHD Rating Scale IV; CI, confidence interval; LS mean, least-squares mean; PERMP, Permanent Product Measure of Performance test; SD, standard deviation.
[a]Difference (drug minus placebo) in LS mean change from baseline.
[b]Predose 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 a subgroup of Study 4 and not the total population.
*Doses statistically significantly superior to placebo.

Mydayis is formulated in a capsule containing 3 different types of drug-releasing beads. The first is an immediate-release bead to allow drug levels to rise quickly. The second is a delayed-release bead that releases the drug at a pH of 5.5. The third is another delayed-release bead that releases amphetamine at a pH of 7.0. The different pharmacokinetic profiles of the individual beads allow for prolonged delivery of medication through the morning, afternoon, and evening.[15]

Researchers compared subjects taking 37.5 mg capsules of Mydayis with subjects who took 25 mg of MAS-ER, followed by 12.5 mg of an immediate-release amphetamine 8 hours later. With one capsule of Mydayis 37.5 mg, patients achieved similar plasma concentrations as with a dose of MAS-ER (other) 25 mg followed by a dose of 12.5 mg 8 hours later (**Figure 2**).[15]

CLINICAL EFFICACY DATA

Researchers have demonstrated the efficacy of Mydayis through 5 different short-term clinical trials: 3 in adults and 2 in pediatrics aged 13 to 17 years.[15]

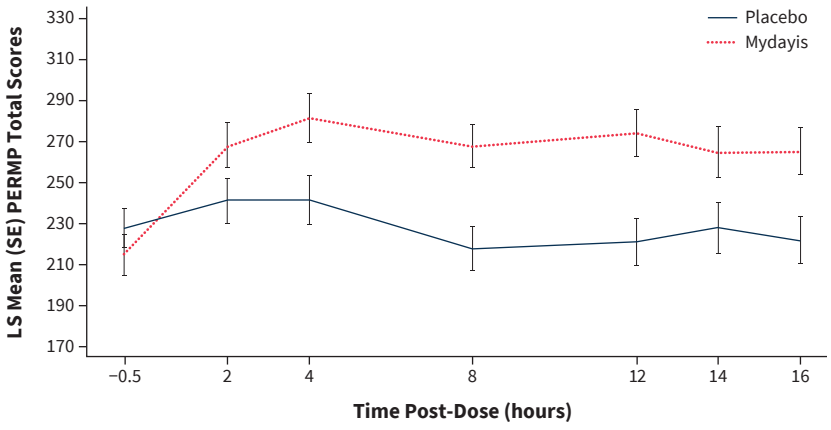
Data in Adults

Study 1 was a 4-week, randomized, double-blind, placebo-controlled study of safety and efficacy in 275 adults (aged 18 to 55 years) with ADHD. Patients were split evenly into 2 treatment groups and a placebo group. Patients in the first treatment group received a 12.5-mg/day dose of Mydayis throughout the study. Patients in the second treatment group received an initial dose of 12.5 mg/day and were titrated weekly until reaching 37.5 mg/day by Week 3, and were then maintained at this level.[15]

The primary efficacy endpoint was the change from baseline of the ADHD-RS with adult prompts total score at Week 4. A key secondary endpoint was the Clinical Global Impression of Improvement (CGI-I) compared with placebo. At Week 4, both Mydayis treatment groups demonstrated a statistically significant treatment effect compared with the placebo group, as assessed by both sets of scores (see Study 1 in **Table 5**).[15]

These results were confirmed in 2 randomized, double-blind, placebo-controlled crossover studies of Mydayis at doses of 50

FIGURE 3. LS Mean (SE) PERMP Total Score by Treatment and Time-Point for Pediatrics (13-17 years) With ADHD After 1 Week of Double-Blind Treatment (Study 5)[14]



ADHD indicates attention-deficit/hyperactivity disorder; LS mean, least-squares mean; SE, standard error.

mg/day (see Study 2 in Table 5) and 25 mg/day (see Study 3 in Table 5) in adult patients with ADHD.[15] These studies utilized the Permanent Product Measure of Performance test (PERMP), a skill-adjusted math test measuring attention. Higher scores indicate better attention. Researchers conducted assessments at 2, 4, 8, 12, 14, and 16 hours after taking Mydayis. Patients taking Mydayis in the 50-mg study showed a significantly significant improvement compared with placebo on the PERMP starting at the 2-hour assessment; patients taking Mydayis in the 25-mg study showed such improvement starting at the 4-hour assessment. In both cases, this improvement was sustained in each time-point measured through 16 hours post-dose.[15]

Data in Pediatrics (13-17 years)

A 4-week, randomized, double-blind, placebo-controlled trial examined 157 ADHD patients aged 13 to 17 years (Study 4 in Table 5).[15] Subjects were randomized in a 1:1 ratio to Mydayis or placebo. It is important to note that the studies were not designed to make comparisons between the Mydayis 12.5 mg and 37.5 mg treatment arms. These same subjects were titrated to an optimal dose (up to a maximum of 25 mg), which was then maintained for the rest of the study. The primary efficacy endpoint was the change from baseline of the ADHD-RS-IV total score at Week 4. A key secondary endpoint was the CGI-I score. At Week 4, Mydayis demonstrated a statistically significant treatment effect compared with placebo on both the ADHD-RS and the CGI-I.[15]

Another randomized, double-blind, placebo-controlled crossover trial also examined pediatric patients (13-17 years) with ADHD. Here, researchers again used the PERMP to assess efficacy. Patients in the Mydayis treatment group received 25 mg/day. Patients in the treatment group showed statistically significant improvement at 6 different assessment points starting at 2 hours up to 16 hours after taking Mydayis compared to placebo (see Study 5 in Table 5 and **Figure 3**).[15]

POTENTIAL FOR OVERDOSE DUE TO MEDICATION ERRORS

Do not substitute Mydayis with other amphetamine products on a milligram-per-milligram basis. Because of different amphetamine base composition and pharmacokinetic profiles, this could lead to possible overdosage.[15] Patients switching to Mydayis from another medication should first discontinue that treatment and use the standard Mydayis titrating schedule (see Table 2).[15]

WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, AND ADVERSE REACTIONS

Potential for Abuse

CNS stimulants have a high potential for abuse, and clinicians must educate patients on this topic.[15] Patients abusing these drugs may experience cravings, and may use these drugs compulsively, not as prescribed.[15]

The mixed amphetamine salts in Mydayis make it essential that patients understand Mydayis is a controlled substance (CII).[15] Patients must understand that selling or giving away Mydayis may be harmful to others, and is against the law.[15] Patients must also learn how to properly store and dispose of the drug.[15]

Before beginning therapy, clinicians should assess patients for

risk of potential abuse. Clinicians should also keep careful records of prescriptions. It is also important to periodically re-evaluate whether Mydayis is still needed.[15]

Additionally, clinicians should monitor patients for signs of abuse while taking Mydayis. Increased heart rate, respiratory rate, and blood pressure may be signs of amphetamine abuse. Dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, and vomiting are other potential symptoms. Anxiety, hostility, psychosis, and homicidal or suicidal thoughts are also possible.[15] Abusers may administer the drug by other methods, which can result in overdose and death.[15]

Serious Cardiovascular Reactions

Sudden death, stroke, myocardial infarction, and cardiomyopathy have occurred in some adults taking recommended dosages of CNS stimulants such as Mydayis. Some pediatric patients with structural cardiac abnormalities or other serious heart problems have died suddenly while taking CNS stimulants for ADHD as prescribed. Because of this, clinicians should not prescribe Mydayis for patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, coronary artery disease, or other serious heart problems. Before beginning Mydayis, clinicians should carefully assess the likelihood of cardiac disease via patient history, family history of sudden death or ventricular arrhythmia, and physical exam.[15]

Blood Pressure and Heart Rate Increases

CNS stimulants such as Mydayis increase blood pressure and heart rate. The mean blood pressure increase is about 2 to 4 mm Hg, and the mean heart rate increase is about 3 to 6 bpm. Because of this, all patients should be monitored for potential tachycardia and hypertension.[15] Any patient who develops exertional chest pain, unexplained syncope, or arrhythmias during treatment should receive further evaluation.[15] Clinicians should instruct patients to contact a health care provider immediately if they develop symptoms like exertional chest pain.[15]

Psychiatric Adverse Reactions

Physicians should also stay alert to possible psychiatric symptoms in patients taking Mydayis. These might include symptoms of overstimulation, dyskinesia, dysphoria, tics, fatigue, aggression, and paresthesia.[15] An analysis of multiple short-term and placebo-controlled studies of CNS stimulants found that 0.1% of treated patients developed psychotic or manic symptoms, compared with 0% of controls. In patients with a pre-existing psychotic disorder, CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder. In patients with bipolar disorder, CNS stimulants may induce a mixed or manic episode. Prior to initiating treatment, patients should be screened for risk factors for developing a manic episode such as comorbid or history of depressive symptoms, or a family history of suicide, bipolar disorder, and depression.[15]

CNS stimulants at prescribed doses may also induce psychotic or manic symptoms in patients who have no prior history of psychotic illness or mania. Clinicians should discontinue Mydayis in patients who do develop psychotic or manic symptoms, such as hallucinations, delusional thinking, or mania.[15]

Long-Term Growth Suppression

Growth suppression is a concern using CNS stimulants, since these drugs have been associated with weight loss and slowed growth rate in pediatric patients. A 4-week placebo-controlled trial of Mydayis in patients aged 6 to 17 years showed a decreased weight in the Mydayis group compared with the placebo group. Because of these concerns, clinicians should closely monitor weight and height in pediatric patients treated with Mydayis, and should advise patients of the possibility of growth suppression. If necessary, patients should have their treatment interrupted if they are not growing or gaining weight as expected. Mydayis is not approved for patients 12 years or younger.[15]

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Clinicians should be aware that CNS stimulants such as Mydayis are associated with peripheral vasculopathy, including Raynaud's

phenomenon. Typically, these symptoms are intermittent and mild, but very rarely ulceration or soft-tissue breakdown can occur.[15] Because of this, clinicians must carefully monitor digital ulceration and/or soft tissue breakdown. Clinicians should advise patients to be alert for digital changes in coloration, numbness, pain, or sensitivity to temperature.[15] Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports at different times and therapeutic doses in all age groups throughout the course of treatment. Such symptoms generally improve after dose reduction or drug discontinuation. When warranted, certain patients may need referral to specialists for further evaluation.[15]

Seizures

Clinicians should also be aware that Mydayis may lower the convulsive threshold for seizure. This may make seizure more likely both in patients with a prior history of seizure, prior EEG abnormalities in the absence of seizures, and in patients with no such history. Treatment with Mydayis should be stopped if a seizure occurs.[15]

Serotonin Syndrome

Patients taking certain psychiatric drugs along with Mydayis are also at risk of serotonin syndrome.[15] Serotonin syndrome can lead to mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms.[15] Patients should be told to consult a health care provider immediately if such symptoms occur. This potentially life-threatening reaction may occur when amphetamines are used with drugs affecting the serotonergic neurotransmitter systems. These include such drugs as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, triptans, tricyclic antidepressants, and others.[15]

Drugs that are cytochrome P450 2D6 inhibitors may also increase the risk of serotonin syndrome when given in combination with serotonergic drugs. In this scenario, clinicians should consider substituting either an alternative serotonergic drug or a drug that does not inhibit CYP2D6.[15] If serotonin syndrome occurs, clinicians must discontinue Mydayis and serotonergic agents and begin supportive treatment.[15] Because of the risk of hypertensive crisis syndrome, MAOIs are contraindicated while using Mydayis.[15] See Table 4 for more detail on drug interactions.[15]

Potential for Overdose Due to Medication Errors

CNS stimulants such as Mydayis pose a risk of overdose from substitution and dispensing errors, drug interactions, or drug abuse.[15] Symptoms and signs of overdose may vary, so clinicians must retain a high index of suspicion. Symptoms may include restlessness, tremor, hyperreflexia, rapid breathing, confusion, hallucinations, panic states, high fever, rhabdomyolysis, arrhythmias, increased or decreased blood pressure, and gastrointestinal symptoms such as diarrhea. Fatigue and depression may occur after initial CNS stimulation. Convulsions and coma typically precede a fatal overdose.[15]

D-amphetamine is not dialyzable. Certified poison control centers can provide up-to-date guidance for optimized treatment of overdose.[15] To help prevent a tragic outcome, clinicians should instruct patients to seek medical care immediately if an overdose is suspected.[15]

Adverse Reactions

In adults, the safety of Mydayis were pooled from 3 randomized, double-blind, placebo-controlled studies that lasted from 4 to 7 weeks. Patients received dosages ranging from 12.5 mg to 75 mg per day (1.5 times the maximum recommended dosage).

In this pooled data set, 9% (54/626) of adult patients with ADHD treated with Mydayis discontinued treatment due to AEs, compared with 2% (7/328) of patients who received placebo. The AEs that most frequently led patients to stop taking Mydayis were insomnia (2%; n = 15), increased blood pressure (2%; n = 10), decreased appetite (1%; n = 5), and headache (1%; n = 4). Overall, the most common adverse reactions reported by 5% or more of adults (ages 18-55 years) taking Mydayis and that were twice the incidence of patients taking placebo were insomnia, decreased appetite, dry mouth, decreased weight, increased heart rate, and anxiety. **Table 6** lists the AEs that occurred in more than 2% of the Mydayis group, compared with the placebo group.[15]

TABLE 6. Adverse Reactions Reported by 2% or More of Adults Taking Mydayis[15,a]

Body System	Adverse Effect	Mydayis[b] (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			
	Increased heart rate	9%	0%
	Palpitations	4%	2%
Genitourinary system			
	Dysmenorrhea[c]	4%	2%
	Erectile dysfunction[d]	2%	1%

[a]Occurring with at least twice the incidence of that in patients taking placebo in 3 clinical trials (4, 6, and 7 weeks).
[b]Includes doses up to 75 mg (1.5 times the maximum recommended dose).
[c]Dysmenorrhea was observed in 11 females.
[d]Erectile dysfunction was observed in 6 males.

Other physical AEs have been reported with amphetamine use. These include mydriasis, constipation, and alopecia. Other possible skin complications include rash and hypersensitivity reactions, which may be severe. Serious skin rashes such as Stevens-Johnson syndrome have also occurred. Rhabdomyolysis has also been reported.[15]

Safety data for pediatrics (13-17 years) is from a randomized, double-blind, placebo-controlled trial of 78 patients who received 12.5 mg to 25 mg Mydayis. In this group, 5% of patients who were receiving the drug discontinued its use due to AEs, compared with 0% of the placebo-group patients. The most frequent AEs that led patients to stop taking the drug were dizziness (1%; n = 1), depression (1%; n = 1), abdominal pain (1%; n = 1), and viral infection (1%; n = 1). Overall, the most common adverse reactions reported by 5% or more of pediatrics (ages 13-17 years) taking Mydayis and that were twice the incidence of patients taking placebo were decreased appetite, nausea, insomnia, upper abdominal pain, irritability, and decreased weight.[15] See **Table 7** for a list of the AEs that occurred in greater than 2% of treated patients, compared with the placebo group.[15]

Please see accompanying Full Prescribing Information located after page 18.

OVERDOSE HOTLINE

For up-to-date guidance about Mydayis overdose treatment, consult with a Certified Poison Control Center: **1-800-222-1222.**[15]

TABLE 7. Adverse Reactions Reported by ≥2% or More of Adolescents (13-17 years) Taking Mydayis[15,a]

Body System	Adverse Effect	Mydayis (n = 78)	Placebo (n = 79)
Nervous system			
	Dizziness	4%	0%
Psychiatric disorders			
	Irritability	6%	3%
	Insomnia	8%	3%
Metabolism and nutritional disorders			
	Decreased appetite	22%	6%
	Weight decreased	5%	1%
Gastrointestinal system			
	Nausea	8%	4%
	Upper abdominal pain	4%	1%

[a]Adolescents aged 13 to 17 years; at least twice the incidence in patients taking placebo in a 4-week clinical trial.

PREGNANCY, LACTATION, AND FERTILITY

Limited data exist on the safety of amphetamines (including Mydayis) during pregnancy. These data have not established a clear causal connection between prescribed amphetamine use and birth defects or miscarriage.[15] Because amphetamines induce vasoconstriction, they may decrease blood perfusion of the placenta. Amphetamines may also cause uterine contractions. Additionally, adverse pregnancy outcomes such as prematurity and low birth weight may be more likely in infants born to mothers dependent on amphetamines.[15]

Animal studies showed no effects on fetal morphological development or survival when pregnant rats and rabbits received oral amphetamine in the same 1:3 *d*- to *l*-amphetamine ratio present in Mydayis. The rats received approximately the maximum recommended dose of 50 mg/day for adults; the rabbits received approximately 5 times that amount, when adjusted for body surface area. However, in another study, pregnant mice received parenteral *d*-amphetamine at approximately 4 times or greater than the maximum recommended dose for adults, resulting in some cases of fetal malformation and death.[15]

Many studies in the literature indicate that amphetamine at levels similar to clinical doses may result in long-term neurochemical and behavioral alterations in rodents, including learning and memory deficits and changes in motor activity and sexual function.[15] Clinicians should speak to patients about the possible risks of continuing Mydayis during pregnancy.[15]

Breastfeeding is not recommended during treatment with Mydayis because of the potential for AEs in nursing infants. These may include serious cardiovascular reactions and growth suppression. However, data from limited case reports have not revealed AEs on breastfed infants at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage. It is not known if amphetamine exposure during breastfeeding might cause long-term neurodevelopmental effects.[15]

The possible effects of Mydayis on fertility are not fully known. However, in 1 study, rats received amphetamines in the same 1:3 *d*- to *l*- ratio of Mydayis at doses approximately 3 times the maximum recommended dose for adults when compared via body surface area. Such a dose did not adversely affect fertility.[15]

NONCLINICAL TOXICOLOGY

Risk of Carcinogenesis/Mutagenesis

Researchers evaluated the carcinogenicity of amphetamine in a 1:1 *d*- to *l*-amphetamine ratio given orally to mice and rats over 2 years. Doses were given up to 3, 2, and 1 times the maximum recommended dose for adults (50 mg/day) when adjusted for body surface area. These studies found no evidence for carcinogenicity.[15]

Amphetamine in the 1:3 *d*- to *l*- ratio was not found to be clastogenic in the mouse bone marrow micronucleus test and was negative in the *Escherichia coli* component of the Ames test. A 1:1 ratio of amphetamine produced a positive response in the mouse bone marrow micronucleus test; however, it also produced a negative response in the sister chromatid exchange and chromosomal aberration assay.[15]

SUMMARY

The exact mechanism of action of stimulants in ADHD is not known. CNS stimulant medications such as Mydayis are theorized to work by increasing the concentrations of catecholamines in the prefrontal cortex, thereby leading to symptoms improvement in patients with ADHD.[10] Mydayis is a once-a-day, oral CNS stimulant containing amphetamine salts in a 3:1 *d*- to *l*-enantiomeric relationship. Mydayis is indicated for the treatment of ADHD in patients ≥13 years. Patients ≤12 years experienced higher plasma exposure at the same dose and higher rates of adverse reactions, mainly insomnia and decreased appetite.[15]

The efficacy of Mydayis has been established through 5 different trials in adults and adolescents (aged 13-17 years). Mydayis helped patients with ADHD achieve statistically significant improvement in ADHD as measured by changes in the ADHD Rating Scale and the Permanent Product Measure of Performance test.[15] Furthermore, Mydayis helped improve attention up to 16 hours post-dose (onset 2 or 4 hours), with once daily dosing. In both adults and adolescents, analysis based on gender or race did not reveal any differences.[15]

CNS stimulants, including Mydayis, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence, which is why it is important to assess the risk of abuse prior to prescribing and then monitor for signs of abuse and dependence during treatment.[15]

Refer to the Full Prescribing Information beginning on the next page for more efficacy and safety information on Mydayis.

REFERENCES

1. Attention-deficit/hyperactivity disorder. In: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

2. Briars L, Todd T. A review of pharmacological management of attention-deficit/hyperactivity disorder. *J Pediatr Pharmacol Ther*. 2016;21(3):192-206. doi: 10.5863/1551-6776-21.3.192.

3. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *J Am Acad Child Adolesc Psychiatry*. 2014;53(1):34-46.e2. doi: 10.1016/j.jaac.2013.09.001.

4. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *J Child Psychol Psychiatry*. 2014;55(5):436-445. doi: 10.1111/jcpp.12170.

5. Classi P, Milton D, Ward S, Sarsour K, Johnston J. Social and emotional difficulties in children with ADHD and the impact on school attendance and healthcare utilization. *Child Adolesc Psychiatry Ment Health*. 2012;6(1):33. doi: 10.1186/1753-2000-6-33.

6. Cuffe SP, Visser SN, Holbrook JR, et al. ADHD and psychiatric comorbidity: functional outcomes in a school-based sample of children. *J Atten Disord*. 2015 [ePub ahead of print]. doi: 10.1177/1087054715613437.

7. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):990-1002.e2. doi: 10.1016/j.jaac.2012.07.008.

8. Antshel KM, Hargrave TM, Simonescu M, Kaul P, Hendricks K, Faraone SV. Advances in understanding and treating ADHD. *BMC Med*. 2011;9:72. doi: 10.1186/1741-7015-9-72.

9. Matthews M, Nigg JT, Fair DA. Attention deficit hyperactivity disorder. *Curr Top Behav Neurosci*. 2014;16:235-266. doi: 10.1007/7854_2013_249.

10. Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC. Update on environmental risk factors for attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep*. 2011;13(5):333-344. doi: 10.1007/s11920-011-0221-3.

11. Jain R, Katic A. Current and investigational medication delivery systems for treating attention-deficit/hyperactivity disorder. *Prim Care Companion CNS Disord*. 2016;18(4). doi: 10.4088/PCC.16r01979.

12. López FA, Leroux JR. Long-acting stimulants for treatment of attention-deficit/hyperactivity disorder: a focus on extended-release formulations and the prodrug lisdexamfetamine dimesylate to address continuing clinical challenges. *Atten Defic Hyperact Disord*. 2013;5(3):249-265. doi: 10.1007/s12402-013-0106-x.

13. Charach A, Fernandez R. Enhancing ADHD medication adherence: challenges and opportunities. *Curr Psychiatry Rep*. 2013;15(7):371. doi: 10.1007/s11920-013-0371-6.

14. Buitelaar J, Medori R. Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants. *Eur Child Adolesc Psychiatry*. 2010;19(4):325-340. doi: 10.1007/s00787-009-0056-1.

15. Mydayis [package insert]. Lexington, MA: Shire.

MYDAYIS

(mixed salts of a single-entity amphetamine product)
extended-release capsules, CII

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 AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **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)**

----------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 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----------

- *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 overdosage situations. If it occurs, discontinue MYDAYIS and initiate supportive treatment. (5.8)

----------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.

Revised: 06/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from full 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 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 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 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 (ages 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), and 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 Patients 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[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 ≥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 in*somnia 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 Contraindications (4)]*.
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 the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.7)]*.
Examples	Selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
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/m^2 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/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

Safety and effectiveness in pediatric patients with ADHD ages 13 to 17 years has 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 MHRD 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 other 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 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 following prolonged high-dosage administration 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 overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. 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.

	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 gelatin 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.

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.

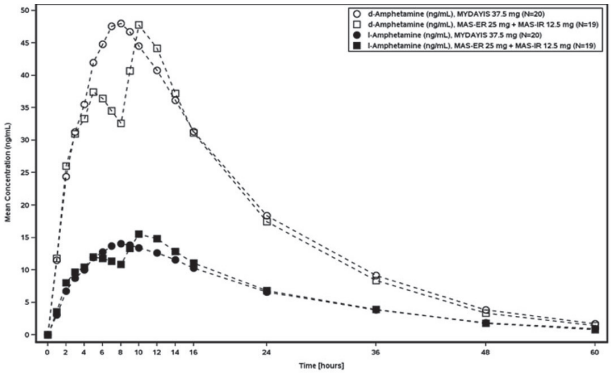
12.3 Pharmacokinetics

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-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%-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 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, 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).

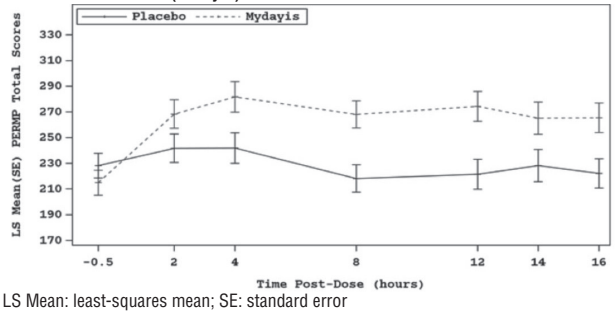
Pediatric patients (13 to 17 years) with ADHD

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)* 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 (18-55 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 (18-55 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 (13-17 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 (13-17 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.
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:

- MYDAYIS capsules 12.5 mg: Green body/green cap (imprinted with black SHIRE 465 and 12.5 mg), bottles of 100, NDC 54092-468-01
- MYDAYIS capsules 25 mg: Ivory body/green cap (imprinted with black SHIRE 465 and 25 mg), bottles of 100, NDC 54092-471-01
- MYDAYIS capsules 37.5 mg: Ivory body/caramel cap (imprinted with black SHIRE 465 and 37.5 mg), bottles of 100, NDC 54092-474-01
- MYDAYIS capsules 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]*.

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

US Pat No. RE41148, US Pat No. RE42096, US Pat. No. US 6913768,
US Pat. No. 8,846,100, and US Pat. No. 9,173,857

Shire

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 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.

- **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.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration

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Notes