DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE- dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate capsule, extended release

Teva Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE EXTENDED-RELEASE CAPSULES.

DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE (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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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

- Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules should be administered once daily upon awakening.

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. (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 preexisting 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. (5.7)
- *Serotonin Syndrome:* Increased risk when coadministered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 Teva at 1-888-838-2872 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule dosage accordingly. (2.5, 7.1)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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

Dextroamphetamine saccharate, amphetamine aspartate monohydrate,

dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules use *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9)].*

2.2 General Instructions for Use

Because the effects of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules and adjust dosage as needed.

2.3 Administration Instructions

Administer dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules orally with or without food. Advise patients to take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules consistently either with food or without food *[see Clinical Pharmacology (12.3)].*

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may be administered in one of the following ways:

- Swallow dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules is 12.5 mg daily with a maximum recommended dose of 25 mg daily. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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: orange opaque cap and body, imprinted with A012 on both cap and body in black ink.
- Extended-release capsules 25 mg: green opaque cap and body, imprinted with A025 on both cap and body in black ink.
- Extended-release capsules 37.5 mg: blue-green opaque cap and body, imprinted with A038 on both cap and body in black ink.
- Extended-release capsules 50 mg: blue opaque cap and body, imprinted with A049 on both cap and body in white ink.

4 CONTRAINDICATIONS

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are contraindicated in patients with:

- Known hypersensitivity to amphetamine, or other components of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for potential tachycardia and hypertension *[see Adverse Reactions (6.1)].*

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disorder

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

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms,

e.g., hallucinations, delusional thinking, or mania in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. In a 4-week, placebo-controlled trial of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules in patients ages 6 to 17 years old with ADHD, there was a decrease in weight in the dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 postmarketing 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

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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, dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules should be discontinued.

5.8 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort *[see Drug Interactions (7.1)]*. The coadministration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased

exposure to dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules with MAOI drugs is contraindicated *[see Contraindications (4)]*.

Discontinue treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules *[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.

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules were 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule-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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule-treated patients and at a rate at least twice that of placebo) were insomnia (2%, n = 15), blood pressure increased (2%, n = 10), decreased appetite (1%, n = 5), and headache (1%, n = 4).

In a controlled trial including adolescent patients (13 to 17 years), 5% (4/78) of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule-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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule-treated patients and at a rate at least twice that of placebo) were dizziness (1%, n = 1), depression (1%, n = 1), abdominal pain upper (1%, n = 1), and viral infection (1%, n = 1).

Adverse Reactions Occurring at an Incidence of ≥ 2% and at Least Twice Placebo Among Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsule-Treated Adults in Clinical Trials

The most common adverse reactions reported in adults were insomnia, decreased appetite, dry mouth, decreased weight, heart rate increased, and anxiety. Table 1 lists the adverse reactions that occurred ≥ 2% compared to placebo. The most common adverse reaction (insomnia) generally occurred early during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

Table 1: Adverse Reactions Reported by 2% or More of Adults Taking Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules and at least Twice the Incidence in Patients Taking Placebo in 3 Clinical Trials (4, 6, and 7-Weeks)

Body System	Adverse Reaction	Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules* (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 Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsule-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 Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial

Body System	Adverse Reaction	Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules (N = 78)	Placebo (N = 79)
Nervous System			

	Dizziness	4%	0%
Metabolism and nutrition disorders			
	Decreased appetite	22%	6%
	Weight decreased	5%	1%
Psychiatric disorders			
	Irritability	6%	3%
	Insomnia*	8%	3%
Gastrointestinal disorders			
	Nausea	8%	4%
	Abdominal pain upper	4%	1%

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

6.2 Adverse Reactions Associated with the Use of Amphetamines

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

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

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

Eye Disorders: Mydriasis.

Gastrointestinal: Unpleasant taste, constipation, intestinal ischemia.

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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules initiation or dosage increase. If serotonin syndrome occurs, discontinue dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules and 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 coadministering dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/.

Risk Summary

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

In an embryofetal development study, amphetamine (*d*- to *l*-enantiomer ratio of 3:1, the same as in dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules) 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% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules) 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

8.4 Pediatric Use

Safety and effectiveness of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules in pediatric patients with ADHD ages 13 to 17 years have been established in two placebo-controlled clinical studies *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]*.

Safety and effectiveness of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules have not been established in pediatric patients ages 12 years and younger.

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules haves

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

Growth Suppression

Growth should be monitored during treatment with stimulants, including dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules) 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules) of 2, 6, or 20 mg/kg on days 7 to 13 of age; from day 14 to approximately day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.8, 2, and 8 times the MRHD of 25 mg/day given to children on a mg/m^2 basis. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules contain mixed amphetamine salts, which are in Schedule II.

9.2 Abuse

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are a CNS stimulant that contains mixed amphetamine salts which have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

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

To reduce the abuse of CNS stimulants, including dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a specific dose of a drug results in a reduction of the drug’s desired

and/or undesired effects over time, in such a way that a higher dose of the drug is required to produce the same effect that was once obtained at a lower dose) may occur during the chronic therapy of CNS stimulants including dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. Withdrawal symptoms after abrupt cessation of CNS stimulants include extreme fatigue and depression.

10 OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules should be considered when treating patients with overdose.

D-amphetamine is not dialyzable.

11 DESCRIPTION

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules contain mixed salts of a single-entity amphetamine, a CNS stimulant. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules contain 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 are designed to contain two types of drug extended release pellets. One type of extended release pellets contains an outer coating of drug to immediately release drug upon administration.

	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: ethylcellulose, hypromellose 2910, iron oxide red, iron oxide yellow, methacrylic acid copolymer dispersion; methyl acrylate, methyl methacrylate, and methacrylic acid copolymer; polyethylene glycol 400, polysorbate 80, sugar spheres (which contains corn starch and sucrose), talc, titanium dioxide, and triethyl citrate. The capsule shells contain gelatin, sodium lauryl sulfate, titanium dioxide. In addition, the 12.5 mg capsule shell contains carboxymethylcellulose, iron oxide red, and iron oxide yellow; the 25 mg capsule shell contains carboxymethylcellulose, FD&C Blue #1, iron oxide red, and iron oxide yellow; the 37.5 mg capsule shell contains carboxymethylcellulose, FD&C Blue #1and FD&C Red #40, and iron oxide red; 50 mg capsule shell contains FD&C Blue #1 and FD&C Red #40. The printing ink for 12.5 mg, 25 mg, and 37.5 mg capsule contains ammonium hydroxide, iron oxide black, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution. The printing ink for the 50 mg capsule contains ammonium hydroxide, povidone, propylene glycol, simethicone (which contains dimethicone and silicon dioxide), shellac, sodium

hydroxide, and titanium dioxide.

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

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

Absorption

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules exhibit 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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).

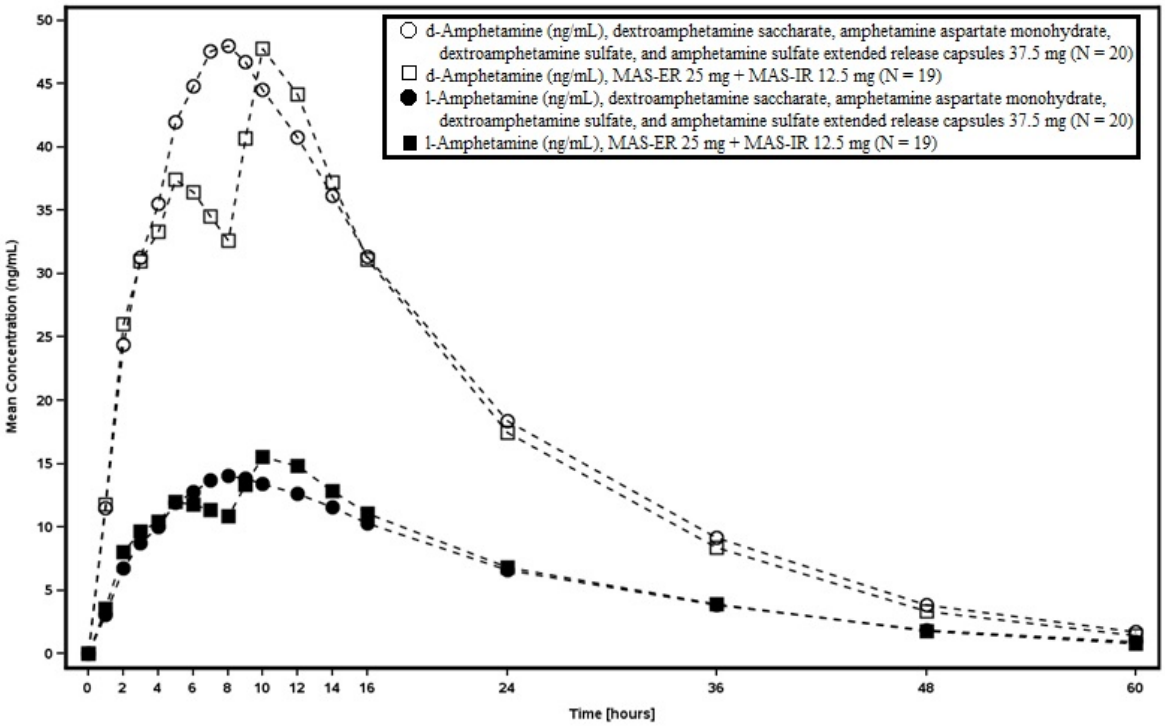


Figure 1: Mean Plasma Concentrations of d- and l-amphetamine Following Oral Administration of Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules 37.5 mg vs MAS-ER 25 mg Followed by Immediate-Release MAS-IR 12.5 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

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

Specific Populations

Age

Comparison of the pharmacokinetics of *d*- and *l*-amphetamine after oral administration of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsule administered to pediatric patients age 13 to 17 years (n = 14) would produce about 21% to 31% higher C_{max} for *d*- and *l*-amphetamine and 21% to 31% higher AUC for *d*- and *l*-amphetamine, compared to the same dose of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules *[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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules dose compared with placebo. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (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).

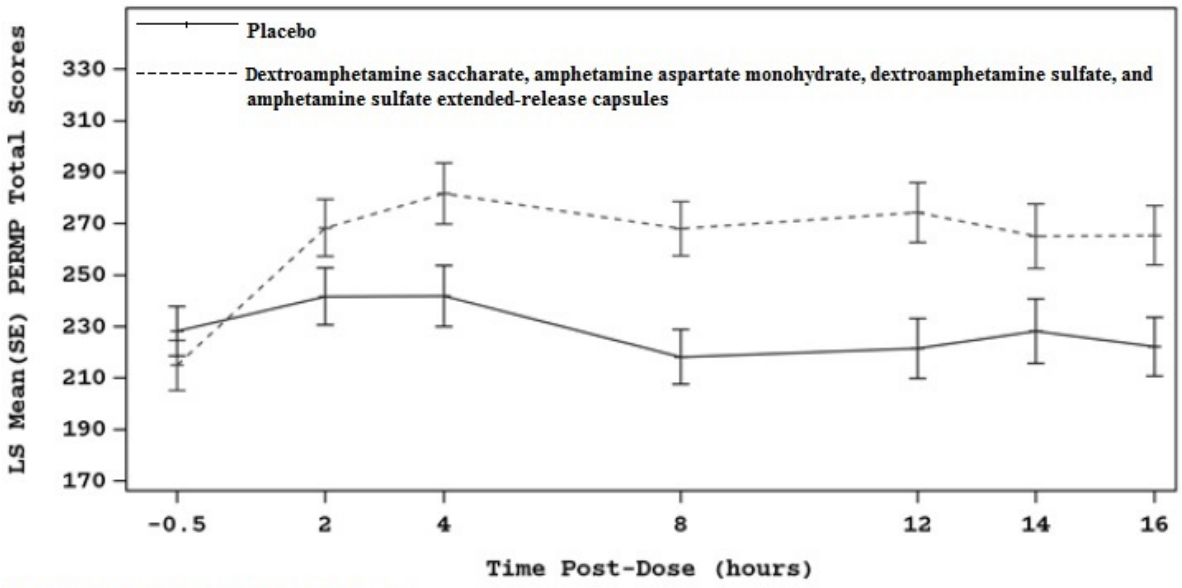
Pediatric patients (13 to 17 years) with ADHD

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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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). Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules treatment, compared to placebo, reached statistical significance at 2 to 16 hours post-dose (Study 5 in Table 4, Figure 2).



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

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)

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 Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Extended-Release Capsules 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		Dextroamphetamine saccharate, amphetamine aspartate monohydrate,	39.8		-8.1 (-11.7, -

Study 1 (18 to 55 years)	ADHD-RS	dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (12.5 mg/day)*	39.8 (6.38)	-18.5	-8.1 (-11.7, -4.4)
		Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (37.5 mg/day)*	39.9 (7.07)	-23.8	-13.4 (-17.1, -9.7)
		Placebo	40.5 (6.52)	-10.4	
Study 2 (18 to 55 years)	Average PERMP	Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (50 mg/day)*	239.2 (75.6)[b]	293.23[c]	18.38 (11.28, 25.47)
		Placebo	249.6 (76.7)[b]	274.85[c]	
Study 3 (18 to 55 years)	Average PERMP	Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (25 mg/day)*	217.5 (59.6)[b]	267.96[c]	19.29 (10.95, 27.63)
		Placebo	226.9 (61.7)[b]	248.67[c]	
Pediatric Studies					
Study 4 (13 to 17 years)[d]	ADHD-RS-IV	Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (12.5 to 25 mg/day)*	36.7 (6.15)	-20.3	-8.7 (-12.6, -4.8)
		Placebo	38.3	-11.6	

		Placebo	(6.67)	-11.0	
Study 5 (13 to 17 years)	Average PERMP	Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules (25 mg/day)*	214.5 (87.8)[b]	272.67[c]	41.26 (32.24, 50.29)
		Placebo	228.7 (101)[b]	231.41[c]	

SD: standard deviation; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Pre-dose PERMP total score.
[c] LS Mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline.
[d] Results represent subgroup of study 4 and not the total population.
* Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are available as:

- 12.5 mg: Orange opaque cap and body, imprinted with A012 on both cap and body in black ink in the following package size:
  Bottle of 100 (NDC 0480-3683-01)

- 25 mg: Green opaque cap and body, imprinted with A025 on both cap and body in black ink in the following package size:
  Bottle of 100 (NDC 0480-3684-01)

- 37.5 mg: Blue-green opaque cap and body, imprinted with A038 on both cap and body in black ink in the following package size:
  Bottle of 100 (NDC 0480-3685-01)

- 50 mg: Blue opaque cap and body, imprinted with A049 on both cap and body in white ink in the following package size:
  Bottle of 100 (NDC 0480-3686-01)

Storage and Handling

Store at 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature].

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

Keep this and all medications out of the reach of children.

Disposal
Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules by a medicine take-back program.
Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release

capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are a federally controlled substance because they can be abused or lead to dependence. Advise patients to store dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine

sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. Further clinical evaluation (e.g. rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Seizures

Caution patient that dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may lower the convulsive threshold. Advise patients to contact their healthcare provider immediately and to discontinue dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules if a seizure occurs *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with concomitant use of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules during pregnancy *[see Use in Specific Populations (8.1)].*

Pregnancy

Advise patients of the potential fetal effects from the use of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules during pregnancy. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules *[see Use in Specific Populations (8.1)].*

Lactation

Advise women not to breastfeed if they are taking dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules *[see Use in Specific Populations (8.2)]*.

Alcohol

Advise patients to avoid alcohol while taking dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. Consumption of alcohol while taking

dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may result in a more rapid release of the dose of mixed amphetamine salts *[see Clinical Pharmacology (12.3)]*.

For more information call Teva at 1-888-838-2872.

Dispense with Medication Guide available at: www.tevausa.com/medguides

Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054

Iss. 10/2022

MEDICATION GUIDE

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Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate
(dex" troe am fet' a meen sak' a rate, am fet' a meen a spar' tate, dex" troe am fet' a meen sul' fate, and am fet' a meen sul' fate)
Extended-Release Capsules, CII
(Mixed Salts of a Single Entity Amphetamine Product)

What is the most important information I should know about dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?

Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules can cause serious side effects, including:

- **Abuse and dependence.** Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.
  - 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

    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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

- **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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What are dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?
Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are 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.
Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are not for use in children 12 years of age and younger.
Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules are a federally controlled substance (CII) because they contain amphetamine that can be a target for people who abuse prescription medicines or street drugs. Keep dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules in a safe place to protect them from theft. Never give dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules to anyone else, because it may cause death or harm them. Selling or giving away dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may harm others and is against the law.

Do not take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules if you or your child are:

- allergic to amphetamine or any of the ingredients in dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. See the end of the Medication Guide for a complete list of ingredients in dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.
- taking, or have taken within the past 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI).

Before taking dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, 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, bipolar illness, or depression

- have circulation problems in fingers and toes
- have or have had seizures
- have kidney problems. You should not take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules if you have end stage renal disease (ESRD).
- are pregnant or plan to become pregnant. It is not known if dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.
  - There is a pregnancy registry for females who are exposed to dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules during pregnancy. The purpose of the registry is to collect information about the health of females exposed to dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules and their baby. If you or your child becomes pregnant during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/research/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate passes into breast milk. You should not breastfeed during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

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.
Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may affect the way other medicines work and other medicines may affect how dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules work. Taking dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules can be taken with other medicines. **Do not start any new medicine during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules without talking to your or your child's healthcare provider first.**

How should I take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?

- Take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.

- Take dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 1 time each day in the morning right after you wake-up. Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may last up to 16 hours and can cause difficulty sleeping.
- If you miss a dose of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, **do not** take your dose later in the day or double your dose to make up for a missed dose. Take your dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules dose the next morning at your regularly scheduled time.
- Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules can be taken with or without food but take them the same way each time.
- Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules may be swallowed whole **or** if dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules treatment for a while to check ADHD symptoms.
- **If you or your child takes too many dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules, call your healthcare provider or go to the nearest hospital emergency room right away.**

What should I avoid during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?
You should avoid drinking alcohol during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

What are possible side effects of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?
Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules can cause serious side effects, including:

- See **"What is the most important information I should know about dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules. Your healthcare provider may stop your child's dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

- **Seizures.** Your healthcare provider will stop treatment with dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules if you have a seizure.
- **Serotonin syndrome.** This problem may happen when dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 movements or muscle twitching
- fast heartbeat
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle stiffness or tightness

The most common side effects of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules include:

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

These are not all the possible side effects of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules.

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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?

- Store dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules from light.
- Store dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules 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 dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make them less appealing to children and pets. Place the mixture in a

container such as a sealed plastic bag and throw away dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules in the household trash.

Keep dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules and all medicines out of the reach of children.

General information about the safe and effective use of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules for a condition for which they were not prescribed. Do not give dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules to other people, even if they have the same condition. They may harm them and it is against the law. You can ask your healthcare provider or pharmacist for information about dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules that was written for healthcare professionals.

What are the ingredients in dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate extended-release capsules?

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

Inactive ingredients: ethylcellulose, hypromellose 2910, iron oxide red, iron oxide yellow, methacrylic acid copolymer dispersion; methyl acrylate, methyl methacrylate, and methacrylic acid copolymer; polyethylene glycol 400, polysorbate 80, sugar spheres (which contains corn starch and sucrose), talc, titanium dioxide, and triethyl citrate. The capsule shells contain gelatin, sodium lauryl sulfate, titanium dioxide. In addition, the 12.5 mg capsule shell contains carboxymethylcellulose, iron oxide red, and iron oxide yellow; the 25 mg capsule shell contains carboxymethylcellulose, FD&C Blue #1, iron oxide red, and iron oxide yellow; the 37.5 mg capsule shell contains carboxymethylcellulose, FD&C Blue #1and FD&C Red #40, and iron oxide red; 50 mg capsule shell contains FD&C Blue #1 and FD&C Red #40. The printing ink for 12.5 mg, 25 mg, and 37.5 mg capsule contains ammonium hydroxide, iron oxide black, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution. The printing ink for the 50 mg capsule contains ammonium hydroxide, povidone, propylene glycol, simethicone (which contains dimethicone and silicon dioxide), shellac, sodium hydroxide, and titanium dioxide.

Manufactured For: **Teva Pharmaceuticals,** Parsippany, NJ 07054
For more information call Teva at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Iss. 10/2022

Package/Label Display Panel

NDC 0480-3683-01

CII

Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate, Dextroamphetamine
Sulfate, and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)Extended-Release Capsules

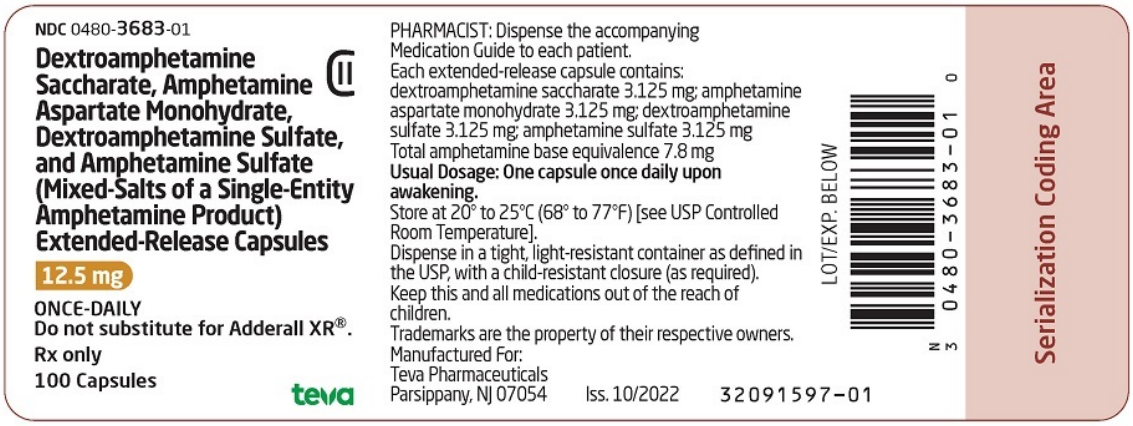
12.5 mg

ONCE-DAILY

Do not substitute for Adderall XR®.

Rx only

100 Capsules



Package/Label Display Panel

NDC 0480-3684-01

CII

Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate, Dextroamphetamine

Sulfate, and Amphetamine Sulfate

(Mixed-Salts of a Single-Entity

Amphetamine Product)

Extended-Release Capsules

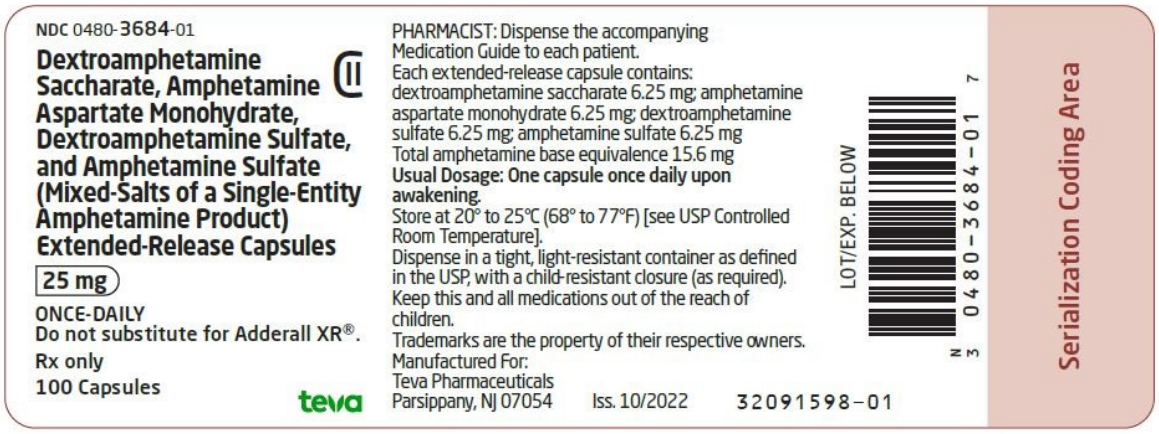
25 mg

ONCE-DAILY

Do not substitute for Adderall XR®.

Rx only

100 Capsules



Package/Label Display Panel

NDC 0480-3685-01

CII

Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate, Dextroamphetamine

Sulfate, and Amphetamine Sulfate

(Mixed-Salts of a Single-Entity

Amphetamine Product)

Extended-Release Capsules

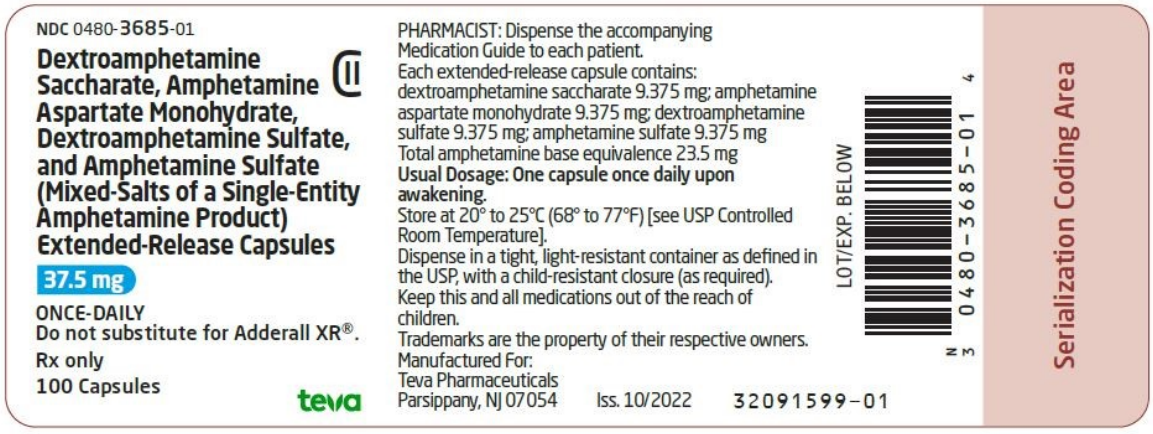
37.5 mg

ONCE-DAILY

Do not substitute for Adderall XR®.

Rx only

100 Capsules



Package/Label Display Panel

NDC 0480-3686-01

CII

Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate, Dextroamphetamine

Sulfate, and Amphetamine Sulfate

(Mixed-Salts of a Single-Entity

Amphetamine Product)

Extended-Release Capsules

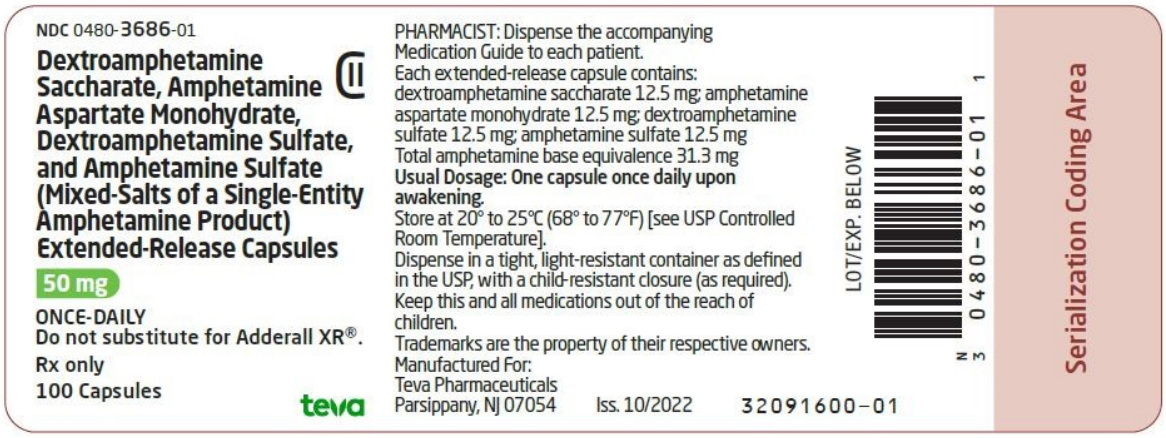
50 mg

ONCE-DAILY

Do not substitute for Adderall XR®.

Rx only

100 Capsules



DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE

dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0480-3683
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DEXTROAMPHETAMINE SACCHARATE (UNII: G83415V073) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SACCHARATE	3.125 mg
AMPHETAMINE ASPARTATE MONOHYDRATE (UNII: O1ZPV620O4) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE ASPARTATE MONOHYDRATE	3.125 mg
DEXTROAMPHETAMINE SULFATE (UNII: JJ768O327N) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SULFATE	3.125 mg
AMPHETAMINE SULFATE (UNII: 6DPV8NK46S) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE SULFATE	3.125 mg

Inactive Ingredients	
Ingredient Name	**Strength**

ETHYLCELLULOSE (10 MPA.S) (UNII: 3DYK7UYZ62)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
METHACRYLIC ACID AND ETHYL ACRYLATE COPOLYMER (UNII: NX76LV5T8J)	
POLY(METHYL ACRYLATE-CO-METHYL METHACRYLATE-CO-METHACRYLIC ACID 7:3:1; 280000 MW) (UNII: 99Q3C7L77T)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CARBOXYMETHYLCELLULOSE (UNII: 05JZI7B19X)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	orange	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	A012;A012
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-3683-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/10/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210876	10/10/2023	

DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE

dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0480-3684
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXTROAMPHETAMINE SACCHARATE (UNII: G83415V073) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SACCHARATE	6.250 mg
AMPHETAMINE ASPARTATE MONOHYDRATE (UNII: O1ZPV620O4) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE ASPARTATE MONOHYDRATE	6.250 mg
DEXTROAMPHETAMINE SULFATE (UNII: JJ768O327N) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SULFATE	6.250 mg
AMPHETAMINE SULFATE (UNII: 6DPV8NK46S) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE SULFATE	6.250 mg

Inactive Ingredients

Ingredient Name	Strength
ETHYLCELLULOSE (10 MPA.S) (UNII: 3DYK7UYZ62)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
METHACRYLIC ACID AND ETHYL ACRYLATE COPOLYMER (UNII: NX76LV5T8J)	
POLY(METHYL ACRYLATE-CO-METHYL METHACRYLATE-CO-METHACRYLIC ACID 7:3:1; 280000 MW) (UNII: 99Q3C7L77T)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CARBOXYMETHYLCELLULOSE (UNII: 05JZI7B19X)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	green	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	A025;A025
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-3684-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/10/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210876	10/10/2023	

DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE

dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0480-3685
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXTROAMPHETAMINE SACCHARATE (UNII: G83415V073) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SACCHARATE	9.375 mg
AMPHETAMINE ASPARTATE MONOHYDRATE (UNII: O1ZPV620O4) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE ASPARTATE MONOHYDRATE	9.375 mg
DEXTROAMPHETAMINE SULFATE (UNII: JJ768O327N) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SULFATE	9.375 mg
AMPHETAMINE SULFATE (UNII: 6DPV8NK46S) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE SULFATE	9.375 mg

Inactive Ingredients

Ingredient Name	Strength
ETHYLCELLULOSE (10 MPA.S) (UNII: 3DYK7UYZ62)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
METHACRYLIC ACID AND ETHYL ACRYLATE COPOLYMER (UNII: NX76LV5T8J)	
POLY(METHYL ACRYLATE-CO-METHYL METHACRYLATE-CO-METHACRYLIC ACID 7:3:1; 280000 MW) (UNII: 99Q3C7L77T)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CARBOXYMETHYLCELLULOSE (UNII: 05JZI7B19X)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	blue (blue-green)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	A038;A038
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-3685-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/10/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210876	10/10/2023	

DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE MONOHYDRATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE

dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0480-3686
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
DEXTROAMPHETAMINE SACCHARATE (UNII: G83415V073) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SACCHARATE	12.500 mg
AMPHETAMINE ASPARTATE MONOHYDRATE (UNII: O1ZPV620O4) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE ASPARTATE MONOHYDRATE	12.500 mg
DEXTROAMPHETAMINE SULFATE (UNII: JJ768O327N) (DEXTROAMPHETAMINE - UNII:TZ47U051FI)	DEXTROAMPHETAMINE SULFATE	12.500 mg
AMPHETAMINE SULFATE (UNII: 6DPV8NK46S) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE SULFATE	12.500 mg

Inactive Ingredients	
Ingredient Name	Strength
ETHYLCELLULOSE (10 MPA.S) (UNII: 3DYK7UYZ62)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
METHACRYLIC ACID AND ETHYL ACRYLATE COPOLYMER (UNII: NX76LV5T8J)	
POLY(METHYL ACRYLATE-CO-METHYL METHACRYLATE-CO-METHACRYLIC ACID 7:3:1; 280000 MW) (UNII: 99Q3C7L77T)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

FD&C RED NO. 40 (UNII: WZB9127XOA)	
AMMONIA (UNII: 5138Q19F1X)	
POVIDONE (UNII: FZ989GH94E)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SHELLAC (UNII: 46N107B71O)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Product Characteristics

Color	blue	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	A049;A049
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-3686-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/10/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210876	10/10/2023	

Labeler - Teva Pharmaceuticals, Inc. (022629579)

Revised: 10/2022 Teva Pharmaceuticals, Inc.