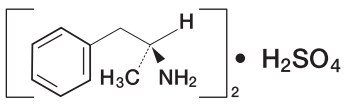
Zenzedi® (dextroamphetamine sulfate, USP) ℂ℡

WARNING
AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINES MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

Dextroamphetamine sulfate, USP is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is *d*-alpha-methylphenethylamine, and is present in all forms of dextroamphetamine sulfate, USP as the neutral sulfate. The structural formula is as follows:



$(C_9H_{13}N)_2 \bullet H_2SO_4$ M.W = 368.49

Each tablet, for oral administration, contains dextroamphetamine sulfate, USP in either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg or 30 mg. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, microcrystalline cellulose and stearic acid.

The 5 mg tablets also contain D&C Red #27 and FD&C Yellow #6. The 7.5 mg tablets also contain FD&C Blue #1 and D&C Yellow #10. The 10 mg tablets also contain FD&C Red #40, FD&C Yellow #6 and FD&C Blue #2. The 15 mg tablets also contain FD&C Blue #1, FD&C Blue #2, and FD&C Red #40. The 20 mg tablets also contain FD&C Blue #1 and D&C Red #27. The 30 mg tablets also contain D&C Yellow #10.

CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine, sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevations of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pharmacokinetics

The pharmacokinetics of the tablet and sustained-release capsule were compared in 12 healthy subjects. The extent of bioavailability of the sustained-release capsule was similar compared to the immediate-release tablet. Following administration of three 5 mg tablets, average maximal dextroamphetamine plasma concentrations (C_{max}) of 36.6 ng/mL were achieved at approximately 3 hours. Following administration of one 15 mg sustained-release capsule, maximal dextroamphetamine plasma concentrations were obtained approximately 8 hours after dosing. The average C_{max} was 23.5 ng/mL. The average plasma T½ was similar for both the tablet and sustained-release capsule and was approximately 12 hours.

In 12 healthy subjects, the rate and extent of dextroamphetamine absorption were similar following administration of the sustained-release capsule formulation in the fed (58 to 75 gm fat) and fasted state.

INDICATIONS AND USAGE

Zenzedi® (dextroamphetamine sulfate tablets, USP) is indicated for:

1. **Narcolepsy.**
2. **Attention Deficit Disorder with Hyperactivity:** As an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in pediatric patients (ages 3 to 16 years) with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Serious Cardiovascular Events

Sudden Death in Patients with Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems.

Children and Adolescents
Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

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

Hypertension and other Cardiovascular Conditions
Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mmHg) and average heart rate (about 3 to 6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia (see CONTRAINDICATIONS).

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications
Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

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

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

Emergence of New Psychotic or Manic Symptoms
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

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

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

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

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants, including Zenzedi, 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 ulcerations and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

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]. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism [see CLINICAL PHARMACOLOGY]. The potential for a pharmacokinetic interaction exists with the coadministration of CYP2D6 inhibitors which may increase the risk with increased exposure to Zenzedi. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 [see Drug Interactions].

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 Zenzedi with MAOI drugs is contraindicated [see CONTRAINDICATIONS].

Discontinue treatment with Zenzedi and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of Zenzedi with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate Zenzedi 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.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

PRECAUTIONS

General

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Information for Patients

Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with dextroamphetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Zenzedi. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]

- Instruct patients beginning treatment with Zenzedi 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 color from pale, to blue, to red.
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- **Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking Zenzedi.**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Drug Interactions

Acidifying Agents – Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamine.

Adrenergic Blockers – Adrenergic blockers are inhibited by amphetamines.

Alkalinizing Agents – Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, Tricyclic – Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; *d*-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of *d*-amphetamine in the brain; cardiovascular effects can be potentiated.

CYP2D6 Inhibitors – The concomitant use of Zenzedi and CYP2D6 inhibitors may increase the exposure of Zenzedi compared to the use of the drug alone and increase the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during Zenzedi initiation and after a dosage increase. If serotonin syndrome occurs, discontinue Zenzedi and the CYP2D6 inhibitor [see WARNINGS, OVERDOSAGE]. Examples of CYP2D6 Inhibitors include paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir.

Serotonergic Drugs – The concomitant use of Zenzedi and serotonergic drugs increases the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during Zenzedi initiation or dosage increase. If serotonin syndrome occurs, discontinue Zenzedi and the concomitant serotonergic drug(s) [see WARNINGS, PRECAUTIONS]. Examples of serotonergic drugs include selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort.

MAO Inhibitors – MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines – Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives – Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine – Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide – Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol – Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effect of amphetamines.

Lithium Carbonate – The stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine – Amphetamines potentiate the analgesic effect of meperidine.

Methenamine Therapy – Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine – Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital – Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin – Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene – In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum Alkaloids – Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

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.

Carcinogenesis/Mutagenesis

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of dextroamphetamine sulfate have not been performed.

Pregnancy

Teratogenic Effects
Pregnancy Category C. Dextroamphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (Vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Dextroamphetamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use

Long-term effects of amphetamines in pediatric patients have not been well established.

Amphetamines are not recommended for use in pediatric patients under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Clinical experience suggests that in psychotic pediatric patients, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder.

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

Data are inadequate to determine whether chronic administration of amphetamines may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the pediatric patient. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the pediatric patient's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS

Cardiovascular

Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System

Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal

Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic

Urticaria.

Endocrine

Impotence, changes in libido, frequent or prolonged erections.

Musculoskeletal

Rhabdomyolysis.

DRUG ABUSE AND DEPENDENCE

Zenzedi is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.

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Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE
Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment
Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

DOSAGE AND ADMINISTRATION
Amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Narcolepsy: Usual dose is 5 to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6 to 12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until an optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Attention Deficit Disorder with Hyperactivity: Not recommended for pediatric patients under 3 years of age.

In pediatric patients from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In pediatric patients 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day.

Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

HOW SUPPLIED
Zenzedi (dextroamphetamine sulfate tablets, USP) is supplied as follows:

2.5 mg: White, square tablet, debossed "2.5" on one side and "MIA" on the other side in bottles of 100 tablets, NDC 24338-850-10.

5 mg: Pink, oval tablet, debossed "5" on one side and "MIA" score on the other side in bottles of 100 tablets, NDC 24338-851-10.

7.5 mg: Light green, triangle tablet, debossed "7.5" on one side and "MIA" on the other side in bottles of 100 tablets, NDC 24338-852-10.

10 mg: Peach, round tablet, double scored on one side and debossed "10" over "MIA" on the other side in bottles of 100 tablets, NDC 24338-853-10.

15 mg: Light blue, pentagon tablet, debossed "15" on one side and "MIA" on the other side in bottles of 100 tablets, NDC 24338-854-10.

20 mg: Purple, capsule-shaped tablet, debossed "20" on one side and "MIA" on the other side in bottles of 100 tablets, NDC 24338-855-10.

30 mg: Light yellow, hexagon tablet, debossed "30" on one side and "MIA" on the other side in bottles of 100 tablets, NDC 24338-856-10.

Dispense in well-closed containers as defined in the USP.

Store at 20° to 25°C (68° to 77°F); excursions permitted 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]

DEA Order Form Required.

Pharmacist: Medication Guide to be dispensed to Patients.

Manufactured for:
Arbor Pharmaceuticals, LLC
Atlanta, GA 30328

arbor PHARMACEUTICALS LLC

MEDICATION GUIDE

Zenzedi® (zen-ZED-ee)
(dextroamphetamine sulfate tablets, USP) Ⓒ

Read the Medication Guide that comes with Zenzedi before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with Zenzedi.

What is the most important information I should know about Zenzedi?

The following have been reported with use of Zenzedi and other stimulant medicines.

1. **Heart-related problems:**
   - **sudden death in patients who have heart problems or heart defects**
   - **stroke and heart attack in adults**
   - **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting Zenzedi.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with Zenzedi.

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

2. **Mental (Psychiatric) problems:**

All Patients
- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

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

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

3. **Circulation problems in fingers and toes** [Peripheral vasculopathy, including Raynaud's phenomenon]:
   - Fingers or toes may feel numb, cool, painful
   - Fingers or toes may change color from pale, to blue, to red

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

Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking Zenzedi.

Zenzedi may not be right for you or your child. Before starting Zenzedi tell your or your child's doctor about all health conditions (or a family history of) including:
- circulation problems in fingers and toes.

What is Zenzedi?
Zenzedi is a central nervous system stimulant prescription medicine. **It is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).**

Zenzedi may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Zenzedi should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Zenzedi is also used in the treatment of a sleep disorder called narcolepsy.

Zenzedi is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep Zenzedi in a safe place to prevent misuse and abuse. Selling or giving away Zenzedi may harm others, and is against the law.

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

Who should not take Zenzedi?
Zenzedi should not be taken if you or your child:
- Have heart disease or hardening of the arteries
- Have moderate to severe high blood pressure
- Have hyperthyroidism
- Have an eye problem called glaucoma
- Are very anxious, tense, or agitated
- Have a history of drug abuse
- Are taking or have taken within the past 14 days an antidepression medicine called a monoamine oxidase inhibitor or MAOI.
- Is sensitive to, allergic to, or had a reaction to other stimulant medicines

Zenzedi is not recommended for use in children less than 3 years old.

Zenzedi may not be right for you or your child. Before starting Zenzedi tell your or your child's doctor about all health conditions (or a family history of) including:
- Heart problems, heart defects, high blood pressure
- Mental problems including psychosis, mania, bipolar illness, or depression
- Tics or Tourette's syndrome
- Thyroid problems
- Seizures or have had an abnormal brain wave test (EEG)

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

Can Zenzedi be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. Zenzedi and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking Zenzedi.

Your doctor will decide whether Zenzedi can be taken with other medicines.

Especially tell your doctor if you or your child take:
- Antidepression medicines including MAOIs
- Blood pressure medicines
- Antacids
- Seizure medicines

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

Do not start any new medicine while taking Zenzedi without talking to your doctor first.

How should Zenzedi be taken?
- **Take Zenzedi exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Zenzedi is usually taken two or three times a day. The first dose is usually taken in the morning. One or two more doses may be taken during the day, 4 to 6 hours apart.
- From time to time, your doctor may stop Zenzedi treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking Zenzedi. Children should have their height and weight checked often while taking Zenzedi. Zenzedi treatment may be stopped if a problem is found during these check-ups.
- **If you or your child take too much Zenzedi or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of Zenzedi?
See **"What is the most important information I should know about Zenzedi?"** for information on reported heart and mental problems.

Other serious side effects include:
- Slowing of growth (height and weight) in children
- Seizures, mainly in patients with a history of seizures
- Eyesight changes or blurred vision
- Serotonin syndrome. A potentially life-threatening problem called serotonin syndrome can happen when medicines such as Zenzedi are taken with certain other medicines. Symptoms of serotonin syndrome may include:
  - agitation, hallucinations, coma or other changes in mental status
  - problems controlling your movements or muscle twitching
  - fast heartbeat
  - high or low blood pressure
  - sweating or fever
  - nausea or vomiting
  - diarrhea
  - muscle stiffness or tightness

Common side effects include:
- Fast heart beat
- Tremors
- Trouble sleeping
- Stomach upset
- Dry mouth
- Decreased appetite
- Headache
- Dizziness
- Weight loss

Zenzedi may affect your or your child's ability to drive or do other dangerous activities. Talk to your doctor if you or your child have side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information. Call your doctor for more medical advice about side effects. You may report side effects to Arbor Pharmaceuticals, LLC, Medical Information at 1-866-516-4950 or FDA at 1-800-FDA-1088.

How should I store Zenzedi?
- Store Zenzedi in a safe place at room temperature, 20° to 25°C (68° to 77°F).
- **Keep Zenzedi and all medicines out of the reach of children.**

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

This Medication Guide summarizes the most important information about Zenzedi. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Zenzedi that was written for healthcare professionals. For more information about Zenzedi you may also contact Arbor Pharmaceuticals, LLC at 1-866-516-4950.

What are the ingredients in Zenzedi?

Active Ingredient: dextroamphetamine sulfate

Inactive Ingredients: colloidal silicon dioxide, crospovidone, microcrystalline cellulose and stearic acid. The 5 mg tablets contain D&C Red #27 and FD&C Yellow #6. The 7.5 mg tablets contain FD&C Blue #1 and D&C Yellow #10. The 10 mg tablets contain FD&C Red #40, FD&C Yellow #6 and FD&C Blue #2. The 15 mg tablets contain FD&C Blue #1, FD&C Blue #2, and FD&C Red #40. The 20 mg tablets contain FD&C Blue #1 and D&C Red #27. The 30 mg tablets also contain D&C Yellow #10.

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

Manufactured by Mikart Inc. Atlanta, GA 30318
for Arbor Pharmaceuticals, LLC, Atlanta, GA 30328.

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Rev. 02/17