RECORDATI RARE DISEASES GROUP

IMPORTANT PRESCRIBING INFORMATION

February 26, 2021

Subject: Shortage of DESOXYN (methamphetamine hydrochloride tablets, USP) 5mg

Dear Health Care Provider,

There has been an unexpected disruption in the manufacturing of DESOXYN (methamphetamine hydrochloride tablets, USP) 5mg approved for use and distribution in the United States, which has resulted in a shortage of this product in the US market. At this point, there is no timeline for the possible return to market for DESOXYN.

U.S. FDA-approved Indication

Attention Deficit Disorder with Hyperactivity: DESOXYN tablets are indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children over 6 years of age 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.

For reporting of adverse events and more information

Any adverse effects or medication issues resulting from the use of this drug or quality issues should be reported to Recordati Rare Diseases Inc. at 1-888-575-8344.

Adverse reactions or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm
- **Regular mail or Fax**: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Important Safety Information

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Methamphetamine has a high potential for abuse. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for non-therapeutic use or distribution to others, and the drug should be prescribed or dispensed sparingly. Misuse of methamphetamine may cause sudden death and serious cardiovascular adverse events.

DESOXYN is contraindicated in patients known to be hypersensitive to amphetamine, or other components of the drug. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products.

DESOXYN is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis. DESOXYN is also contraindicated in patients with glaucoma, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism or known hypersensitivity or idiosyncrasy to sympathomimetic amines. DESOXYN should not be given to patients who are in an agitated state or who have a history of drug abuse.

Sudden Death and 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.

Hypertension and other Cardiovascular Conditions:

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.

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.

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.

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.

Aggression: 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: 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: In the presence of seizures, the drug should be discontinued.

Peripheral Vasculopathy, including Raynaud's phenomenon:
Stimulants, including DESOXYN, 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. 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.

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. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism. The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to DESOXYN. In these situations, consider an alternative nonserotonergic drug or an alternative drug that does not inhibit CYP2D6. 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). Discontinue treatment with DESOXYN and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of DESOXYN with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate DESOXYN 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.

General Precautions: DESOXYN tablets should be used with caution in patients with even mild hypertension. Methamphetamine should not be used to combat fatigue or to replace rest in normal persons. Prescribing and dispensing of methamphetamine should be limited to the smallest amount that is feasible at one time in order to minimize the possibility of overdosage. The patient should be informed that methamphetamine may impair the ability to engage in potentially hazardous activities, such as, operating machinery or driving a motor vehicle. Instruct patients beginning treatment with DESOXYN 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 DESOXYN. The patient should be cautioned not to increase dosage, except on advice of the physician. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methamphetamine and should counsel them in its appropriate use.

Long-term effects of methamphetamine in children have not been established. Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

DESOXYN tablets are subject to control under DEA schedule II.
Abuse: Methamphetamine has 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. Manifestations of chronic intoxication with methamphetamine include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis often clinically indistinguishable from schizophrenia. Abuse and/or misuse of methamphetamine have resulted in death. Fatal

cardiorespiratory arrest has been reported in the context of abuse and/or misuse of methamphetamine.

Overdosage

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. Serotonin syndrome has also been reported. 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 of overdosage

Consult with a Certified Poison Control Center for up to date guidance and advice.

The following are adverse reactions in decreasing order of severity within each category that have been reported:

Cardiovascular: Elevation of blood pressure, tachycardia and palpitation. Fatal cardiorespiratory arrest has been reported, mostly in the context of abuse/misuse.

Central Nervous System: Psychotic episodes have been rarely reported at recommended doses. Dizziness, dysphoria, overstimulation, euphoria, insomnia, tremor, restlessness and headache. Exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal: Diarrhea, constipation, dryness of mouth, unpleasant taste and other gastrointestinal disturbances.

Hypersensitivity: Urticaria.

Endocrine: Impotence and changes in libido; frequent or prolonged erections.

Musculoskeletal: Rhabdomyolysis.

Miscellaneous: Suppression of growth has been reported with the long-term use of stimulants in children.

Skin and Subcutaneous Tissue Disorders: Alopecia.

We are committed to helping address patients' unmet needs through our corporate mission. If you have questions or concerns regarding this product, please call Recordati Rare Diseases Medical Information at 1-888-575-8344.

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