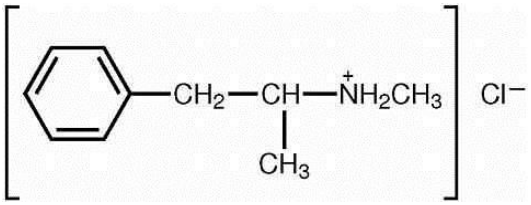
Desoxyn® Ⓒ Ⅱ
(methamphetamine hydrochloride tablets, USP)

Rx only

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.

DESCRIPTION

DESOXYN® (methamphetamine hydrochloride tablets, USP), chemically known as (S)-N,α-dimethylbenzeneethanamine hydrochloride, is a member of the amphetamine group of sympathomimetic amines. It has the following structural formula:



DESOXYN tablets contain 5 mg of methamphetamine hydrochloride for oral administration.

Inactive Ingredients:
Corn starch, lactose, sodium paraminobenzoate, stearic acid and talc.

CLINICAL PHARMACOLOGY

Methamphetamine is a sympathomimetic amine with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. Other central nervous system actions, or metabolic effects, may be involved, for example.

The mechanism of action involved in producing the beneficial behavioral changes seen in hyperkinetic children receiving methamphetamine is unknown.

In humans, methamphetamine is rapidly absorbed from the gastrointestinal tract. The primary site of metabolism is in the liver by aromatic hydroxylation, N-dealkylation and deamination. At least seven metabolites have been identified in the urine. The biological half-life has been reported in the range of 4 to 5 hours. Excretion occurs primarily in the urine and is dependent on urine pH. Alkaline urine will significantly increase the drug half-life. Approximately 62% of an oral dose is eliminated in the urine within the first 24 hours with about one-third as intact drug and the remainder as metabolites.

INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

In patients known to be hypersensitive to amphetamine, or other components of DESOXYN. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products (see **ADVERSE REACTIONS**).

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 (see **WARNINGS** and **DRUG INTERACTIONS**). It 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. Methamphetamine should not be given to patients who are in an agitated state or who have a history of drug abuse.

WARNINGS

Serious Cardiovascular Events

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: Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 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.

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 3482 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 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. 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 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 (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 DESOXYN with MAOI drugs is contraindicated (see **CONTRAINDICATIONS**).

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.

PRECAUTIONS

General: 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.

Information for Patients: 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.

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

- 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.**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

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. A patient Medication Guide is available for DESOXYN. 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 available at www.recordatirarediseases.com.

Drug Interactions: Insulin requirements in diabetes mellitus may be altered in association with the use of methamphetamine and the concomitant dietary regimen.

Methamphetamine may decrease the hypotensive effect of *guanethidine*.

DESOXYN should not be used concurrently with *monoamine oxidase inhibitors* (see **CONTRAINDICATIONS**).

Concurrent administration of *tricyclic antidepressants* and indirect-acting sympathomimetic amines such as the amphetamines, should be closely supervised and dosage carefully adjusted.

Phenothiazines are reported in the literature to antagonize the CNS stimulant action of the amphetamines.

Drug/Laboratory Test Interactions: Literature reports suggest that amphetamines may be associated with significant elevation of plasma corticosteroids. This should be considered if determination of plasma corticosteroid levels is desired in a person receiving amphetamines.

Acidifying Agents
Lower blood levels and efficacy of amphetamines. Increase dose based on clinical response. Examples of acidifying agents include gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid) and urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).

Alkalinizing Agents
Increase blood levels and potentiate the action of amphetamine. Co-administration of DESOXYN and gastrointestinal alkalinizing agents should be avoided. Examples of alkalinizing agents include gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) and urinary alkalinizing agents (e.g., acetazolamide, some thiazides).

Tricyclic Antidepressants
May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. Monitor frequently and adjust or use alternative therapy based on clinical response. Examples of tricyclic antidepressants include desipramine, Protriptyline.

CYP2D6 Inhibitors
The concomitant use of DESOXYN and CYP2D6 inhibitors may increase the exposure of DESOXYN 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 DESOXYN initiation and after a dosage increase. If serotonin syndrome occurs, discontinue DESOXYN 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 DESOXYN 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 DESOXYN initiation or dosage increase. If serotonin syndrome occurs, discontinue DESOXYN and the concomitant serotonergic drug(s) (see **WARNINGS** and **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
Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure. Do not administer DESOXYN concomitantly or within 14 days after discontinuing MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). Examples of MAOIs include selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue.

Proton Pump Inhibitors
Time to maximum concentration (Tmax) of amphetamine is decreased compared to when administered alone. Monitor patients for changes in clinical effect and adjust therapy based on clinical response. An example of a proton pump inhibitor is omeprazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Data are not available on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

Pregnancy

Teratogenic effects: Pregnancy Category C. Methamphetamine has been shown to have teratogenic and embryocidal effects in mammals given high multiples of the human dose. There are no adequate and well-controlled studies in pregnant women. DESOXYN tablets should not be used during pregnancy unless 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.

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

Long-term effects of methamphetamine in children have not been established (see **WARNINGS**).

Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe DESOXYN tablets should depend on the physician's assessment of the chronicity and severity of the child'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 DESOXYN tablets is usually not indicated.

Clinical experience suggests that in psychotic children, administration of DESOXYN tablets 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 children and their families should precede use of stimulant medications.

Geriatric Use: Clinical Studies of DESOXYN did not include sufficient numbers of subjects age 65 years and over to determine whether elderly subjects 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 be cautious, usually starting 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 observed in this population.

ADVERSE REACTIONS

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 (see **WARNINGS**).

Skin and Subcutaneous Tissue Disorders: Alopecia.

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: 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

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

DOSAGE AND ADMINISTRATION

DESOXYN tablets are given orally.

Methamphetamine should be administered at the lowest effective dosage, and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity: *For treatment of children 6 years or older with a behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity:* an initial dose of 5 mg DESOXYN once or twice a day is recommended. Daily dosage may be raised in increments of 5 mg at weekly intervals until an optimum clinical response is achieved. The usual effective dose is 20 to 25 mg daily. The total daily dose may be given in two divided doses daily.

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

DESOXYN (methamphetamine hydrochloride tablets, USP) is supplied as white tablets imprinted with the letter R on one side and the number 12 on the opposite side, containing 5 mg methamphetamine hydrochloride in bottles of 100
(NDC 55292-0104-01).

Recommended Storage: Store at 20-25°C (68-77°F). See USP controlled room temperature.
Dispense in a USP tight, light resistant container.

Manufactured by:
UPM Pharmaceuticals
510 5th Street, Bristol, TN 37620, U.S.A.

For: Key Therapeutics, LLC., Flowood, MS 39232, U.S.A.

This product label may have been updated. For the most recent prescribing information, please visit www.keyrx.com

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