Product Information

DEXAMPHETAMINE TABLETS

DRUG DEPENDENCE: Dexamphetamine should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abuse use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour.

NAME OF THE MEDICINE

Dexamphetamine tablets contain the dextro isomer of the compound d,l-amphetamine sulfate, a sympathomimetic amine of the amphetamine group.

DESCRIPTION

Chemically, dextroamphetamine is (s)-alpha-methylphenethylamine sulphate with a chemical formula of \((C_{19}H_{13}N)_{2}H_{2}SO_{4}\) and a molecular weight of 368.5. It is soluble approximately 1:10 in water, 1:500 in alcohol 95% and readily soluble in acids. The structure is represented below:

![Chemical Structure]

CAS No. 51-63-8

Dexamphetamine tablets contain as the active ingredient 5 mg of dextroamphetamine sulfate and the following inert ingredients: lactose, povidone, starch-wheat and magnesium stearate.

PHARMACOLOGY

Amphetamines are non-catecholamine, sympathomimetic amines with central nervous system (CNS) stimulant activity. Dexamphetamine stimulates both alpha and beta-adrenergic receptors. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. It has pronounced stimulation of the central cortex and the respiratory and vasomotor centres. It increases motor activity, mental, wakefulness and produces euphoria.

The exact mechanism of action has not been established, however, in animals, amphetamines facilitate the action of dopamine and noradrenaline by blocking re-uptake from the synapse, inhibit the action of monoamine oxidase (MAO), and facilitate the release of catecholamines. There is no specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioural effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.
Tolerance and dependence of the amphetamine type develop on repeated administration of Dexamphetamine.

**Pharmacokinetics**

Amphetamines are rapidly absorbed from the gastro-intestinal tract reaching peak levels in approximately 2 hours post-administration and have an apparent volume of distribution of 2-3L/Kg body weight. Dexamphetamine is concentrated in the brain, lung and kidneys. Thirty to forty percent is metabolised by the liver, and the hydroxylated metabolite may be responsible for the psychotic effect; the remainder (60 to 70 %) is excreted directly by the kidneys. The approximate plasma half-life is 10.25 hours however, excretion of dexamphetamine is enhanced in an acid urine and slowed in an alkaline urine. The half-life is 16-31 hours in urine with a pH of more than 7.5 and falls to 6-8 hours when the urinary pH is 5.0 or less. The average urinary recovery is 45% in 48 hours.

**INDICATIONS**

Narcolepsy and hyperkinetic behaviour disorders in children.

**CONTRAINDICATIONS**

Cardiac arrhythmia, patients with symptomatic cardiovascular disease including those with a history of myocardial infarction. Severe angina pectoris and ischaemic heart disease, moderate to severe hypertension, hyperthyroidism, phaeochromocytoma, known hypersensitivity or idiosyncrasy to dexamphetamine, sympathomimetic amines, glaucoma, motor tics and Tourette syndrome.

Anxiety, tension, and agitation. Patients who currently exhibit severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency.

Patients with known drug dependence or alcohol abuse.

Concurrent treatment with or within 14 days following the administration of mono amine oxidase inhibitors (hypertensive crises may result, see Drug Interactions).

Allergy to any of the excipients.

**PRECAUTIONS**

Note: Because of the liability for abuse, drugs of the amphetamine type are subject to special restrictions on their availability. Prescriptions of this substance may require validation by State or Territory Health Departments of Commissions.

**Warning of Drug Abuse**

Amphetamines have a high potential for drug abuse. Care should be exercised in the selection of patients for amphetamine therapy and prescription size should be limited to that required to achieve the therapeutic goal. Patients should be cautioned against increasing the recommended dosage. Should psychological dependence occur, gradual withdrawal of the medication is recommended. Abrupt cessation following prolonged high dosage results in
extreme fatigue and mental depression; changes have also been noted on the sleep EEG. 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.

Pre-treatment Assessment

Before starting treatment with Dexamphetamine, it is important to consider the patient’s personal and family cardiac and psychiatric history. In patients with identified or potential cardiovascular or psychiatric risk factors, further investigation or specialist review may be considered.

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. 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.

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.

It is essential that children, adolescents, or adults with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a cardiologist before initiating treatment. Ongoing cardiological supervision should be maintained throughout treatment in these patients.

Hypertension and Other Cardiovascular Disease

According to the FDA’s voluntary Adverse Event Reporting System (AERS) database for the period January 1992 to February 2005, 7 of the 14 cases of sudden death in children and
adolescents occurred during or shortly after exercise, or in association with hyperthermia and dehydration. However, exercise is almost universal in children and this does not necessarily indicate a true association. Nevertheless, due to the effects on the sympathetic nervous system, Dexamphetamine should be used with caution in patients who are involved in strenuous exercise or activities, use stimulants, or have a family history of sudden/cardiac death or life-threatening arrhythmia.

Dexamphetamine should be used with caution in patients with mild hypertension, and in such patients, blood pressure should be monitored more frequently than usual. Because Dexamphetamine can increase blood pressure and heart rate, it is not recommended in patients with conditions which may be aggravated by an increase in blood pressure or heat rate.

**Aggressive Behaviour**

Emergent aggressive behaviour or a worsening of baseline aggressive behaviour has been reported during stimulant therapy. However, patients with ADHD may experience aggression as part of their medical condition. Therefore, causal association with treatment is difficult to assess. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate.

**Depression, Bipolar Disorders or Psychosis**

Administration of Dexamphetamine may exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Prior to initiating treatment with Dexamphetamine, patients with co-morbid 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.

In patients with a past history of or concurrent depression, bipolar disorder or psychosis, Dexamphetamine should be used under close supervision and the patient should be closely observed for worsening of depression or the development of suicidal thoughts or behaviour, or thoughts or acts of self-harm. Treatment with Dexamphetamine should be withdrawn in patients who develop suicidal ideation or behaviour, thoughts or acts of self-harm, psychosis/mania, or worsening of aggression/violent behaviour, and treatment should be reintroduced with caution following recovery.

Particular care should be taken in using Dexamphetamine to treat ADHD in patients with co-morbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

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 Dexamphetamine at usual doses.

**Seizures**
There is some clinical evidence that Dexamphetamine 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.

**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 older than 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 Dexamphetamine 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 Dexamphetamine, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

**Motor tics or Tourette’s Syndrome**

Use with caution in patients with a family history of motor tics or Tourette syndrome.

**Regular Review**

Blood pressure, cardiovascular status and psychiatric status should be reviewed regularly during treatment with Dexamphetamine. Children on Dexamphetamine should have their growth monitored, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

**Effect on Ability to Drive or Operate Machinery**

Dexamphetamine, like all amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles and should be cautioned accordingly.

**Renal Impairment**

Use with caution in renal insufficiency.

**Carcinogenicity and Mutagenicity**

Carcinogenicity and mutagenicity studies and long term studies in animals to determine the carcinogenicity potential of dextroamphetamine sulfate have not been performed.

**Use in Pregnancy** - Pregnancy Category B3.
Dexamphetamine has been shown to have embryotoxic and teratogenic effects in A/Jax and C57B1 mice. Although there are no adequate and well-controlled studies in pregnant woman, the use of amphetamines during early pregnancy may be associated with an increased risk of congenital malformations. Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. These infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and lassitude. Dexamphetamine should not be used by women who are pregnant, and women should be advised to avoid pregnancy during therapy with this drug.

**Use in Lactation**

Amphetamines are excreted in human milk and mothers should be advised to refrain from breast feeding infants.

**Paediatric**

Long term effects of amphetamines in children have not been well established and use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity is not recommended. (see Dosage and Administration).

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

**Use in the Elderly**

There is no information available on use in the elderly.

**DRUG INTERACTIONS**

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

**Alkalising Agents:**
Gastrointestinal alkalising agents (sodium bicarbonate etc) increase absorption of amphetamines. Urinary alkalising agents (acetazolamide and some thiazides) increase the concentration of the non-ionised species of the amphetamine molecule thereby decreasing urinary excretion.

**Adrenergic Agents:**
Adrenergic blockers are inhibited by amphetamines.

**Antidepressants, Tricyclic:**
Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protryptaline and possibly other tricyclics cause striking and sustained release in the concentration of noradrenaline in the brain; the adverse cardiovascular effects of tricyclic antidepressants can be potentiated.
Monoamine Oxidase Inhibitors (MAOI):
MAOI antidepressants slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of noradrenaline 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 (see Contraindications).

Antihistamines:
Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives:
Amphetamines may antagonise the hypotensive effects of antihypertensives.

Chlorpromazine:
Chlorpromazine blocks dopamine and noradrenaline uptake, 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 noradrenaline re-uptake, thus inhibiting the central stimulant effects of amphetamines.

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

Pethidine:
Amphetamines potentiate the analgesic effect of pethidine.

Methenamine Therapy:
Urinary excretion of amphetamine is increased and efficacy is reduced by the acidifying agents used in methenamine therapy.

Adrenaline:
Amphetamines enhance the adrenergic effect of noradrenaline/adrenaline.

Phenobarbitone:
Amphetamines may delay intestinal absorption of phenobarbitone; co-administration of phenobarbitone may produce a synergistic anticonvulsant action.

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

Dextropropoxyphene:
In cases of dextropropoxyphene overdosage, amphetamine CNS stimulation may be potentiated and fatal convulsions could occur.

Drug/Laboratory Test Interactions
Amphetamines can cause a significant elevation in plasma corticosteroid levels (this increase is greatest in the evening) and may interfere with urinary steroid determinations.

**ADVERSE EFFECTS**

**Cardiovascular:**
Palpitations, tachycardia, Raynaud’s phenomenon in susceptible individuals, elevation of blood pressure and some reports of cardiomyopathy associated with chronic amphetamine use.

**Central Nervous System (CNS):**
Psychotic episodes at recommended doses (uncommon), overstimulation, restlessness, dizziness, insomnia, dyskinesia, tremor, headache, exacerbation of motor and phonic tics and Tourette’s syndrome.

**Psychiatric:**
Causality in relation to suicidality, psychosis/mania and aggression/violence has not been established, although these events tend to be supported by post-marketing reports of positive rechallenge with Dexamphetamine. Therefore, adverse psychiatric events are regarded as potential, but very rare effects at normal therapeutic doses of Dexamphetamine.

**Gastrointestinal:**
Mouth dryness, unpleasant taste, diarrhoea, constipation, other gastrointestinal disturbances.

**Allergic:** Urticaria

**Endocrine:** Impotence, changes in libido.

**Other:** Anorexia and weight loss

**DOSAGE AND ADMINISTRATION**

Dexamphetamine should be started at the lowest possible dose and should then be individually and slowly adjusted to the lowest effective dose for each individual.

Time of administration should receive special attention because of insomnia. Late evening medication should be avoided.

**Narcolepsy:**
The usual daily dose ranges from 5 to 60 mg (given in divided doses) for optimal response. If bothersome adverse reactions appear (e.g. insomnia or anorexia) reduce the dosage. In patients from 6 to 12 years of age, start with 5mg daily. The dosage may be raised in increments of 5mg at weekly intervals until the optimal response is obtained. In patients 12 years or older, start with 10 mg daily. The daily dosage may be raised in increments of 10 mg at weekly intervals until the optimal response is obtained.

**Attention Deficit Disorder (Hyperkinetic activity behaviour disorders):**
Not recommended for children under 3 years of age.
In children over 3 years of age start with 2.5 mg daily. Then the daily dosage may be raised in 2.5 mg increments, at weekly intervals, until the optimal response is obtained, up to a maximum of 40 mg daily in two divided doses. The first dose should be given on awakening and any additional dose given 4 to 6 hours later.

Where possible, drug administration should be interrupted occasionally to determine if there is an occurrence of behaviour symptoms sufficient to require continued therapy.

If therapy is recommenced after discontinuation it should not be restarted at the dose that had been reached prior to treatment interruption, but should be re-titrated from the usual starting dose.

**OVERDOSAGE**

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

Symptoms include dilated and reactive pupils, shallow rapid respiration, rhabdomyolysis, fever, chills, sweating, hyperactive tendon reflexes. Central effects may include restlessness, aggressiveness, anxiety, confusion, delirium, hallucinations, panic attacks and suicidal or homicidal tendencies. The stimulant effect is usually followed by depression, lethargy, exhaustion. Cardiovascular effects may include anginal pain, extrasystoles, and other arrhythmias, flushing, headache, hypertension, or hypotension, pallor, palpitations, tachycardia. Circulatory collapse and syncope may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

**Drug Abuse and Dependence:**

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 results in extreme fatigue and mental depression; changes are also noted on sleep EEG.

Manifestations of chronic intoxication with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, aggression, hallucinations, panic states, 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 uncommon with oral amphetamines.

**Treatment of Acute Intoxication:**

Treatments of overdoses are usually symptomatic. Emergency stabilization is required to manage those suffering seizure, cardiac arrest, or the acute consequences of arteriospasm or rupture such as stroke.

Efficacy has not been proven for the use of activated charcoal and should only be considered
in cases of life threatening overdoses. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube, once the airway is protected. In case of massive overdose, whole bowel irrigation (iso-osmotic polyethylene glycol electrolyte solution) may be beneficial, but is not otherwise recommended. Insufficient data is available to recommend the use of haemodialysis or peritoneal dialysis.

Please contact the Poisons Information Centre on 13 11 26 (Australia) for further advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Dexamphetamine tablets are available as a round, white, scored tablet marked D5 packed in containers of 100 tablets.

Store below 25 degrees Celsius.

POISON SCHEDULE OF THE MEDICINE: S8 (Controlled Drug)

NAME AND ADDRESS OF THE SPONSOR

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