PRODUCT MONOGRAPH

APO-DEXTROAMPHETAMINE SR

Dextroamphetamine sulfate sustained release capsules
10 mg and 15 mg capsules

Apotex Standard

Sympathomimetic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	capsule (sustained release) 10 mg, 15 mg	Colloidal silicon dioxide, ethylcellulose, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6, gelatin, hydroxypropyl cellulose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide.

INDICATIONS AND CLINICAL USE

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) is indicated:

- in the adjunctive treatment of narcolepsy
- for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Attention Deficit Hyperactivity Disorder (ADHD)

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing,

difficulty with quiet activities, “on the go,” excessive talking, blurting answers, can’t wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

APO-DEXTROAMPHETAMINE SR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational and social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician’s assessment of the chronicity and severity of the patient’s symptoms.

Long-term Use

The physician who elects to use APO-DEXTROAMPHETAMINE SR for extended periods should periodically re- evaluate the long-term usefulness of the drug for the individual patient.

Geriatrics (> 65 years of age):

The safety and efficacy of APO-DEXTROAMPHETAMINE SR in this patient population have not been established.

Pediatrics (< 18 years of age):

Amphetamines are not recommended for use in Attention-Deficit Hyperactivity Disorder in children under 6 years of age, since safety and efficacy in this age group have not been established. Long-term effects of amphetamines in children above 6 years of age have not been well established.

CONTRAINDICATIONS

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) is contraindicated in patients with:

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Hyperthyroidism
- Hypersensitivity or idiosyncrasy to sympathomimetic amines
- Agitated state
- History of drug abuse
- Glaucoma
- Anxiety
- Tension
- Hypersensitivity to APO-DEXTROAMPHETAMINE SR or to any ingredient in the formulation or component of the container. For complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Motor tics or with a family history of diagnosis of Tourette's Syndrome (verbal tics).
- Concomitant treatment with MAO inhibitors or within 14 days following the withdrawal of MAO inhibitors (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Amphetamines have a potential for abuse and diversion that physicians should consider when prescribing this product (see **Dependence/Tolerance** section below).

General

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. APO-DEXTROAMPHETAMINE SR should be used with caution in patients who use other sympathomimetic drugs.

Cardiovascular

Misuse and Serious Cardiovascular Adverse Events

The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Sudden Death and Pre-existing Structural Cardiac Abnormalities

Children and Adolescents

Sudden death has been reported in association with stimulant drugs used for ADHD 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 2-4 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 (see **CONTRAINDICATIONS**).

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other stimulants or c) have a family history of sudden/cardiac death. 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.

Dependence/Tolerance

Amphetamines have been subject to extensive abuse. Tolerance, extreme psychological dependence, and severe social disability can occur. Patients have been reported to increase their dosage to many times the recommended level. The smallest possible amount of the drug should be prescribed or dispensed at one time.

The possibility of tolerance and psychological dependence, particularly with excessive use, should be kept in mind. Therefore, care should be used in the selection of candidates for APO-DEXTROAMPHETAMINE SR therapy. Should psychological dependence occur, discontinue medication. Abrupt cessation following prolonged high dosage administration may result in extreme fatigue and mental depression. Changes have also been noted on the sleep EEG. Careful supervision is therefore recommended during drug withdrawal.

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.

Endocrine and Metabolism

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.

Neurologic

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.

Effects on Ability to Drive and Use Machinery

Amphetamines may mask extreme fatigue, which can impair the ability to perform potentially hazardous activities such as operating machinery or driving motor vehicles;

patients should be cautioned accordingly.

Tics

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

Ophthalmologic

Visual Disturbances

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. Glaucoma is a contraindication of APO-DEXTROAMPHETAMINE SR and should be ruled out if visual disturbance occurs (see **CONTRAINDICATIONS)**.

Psychiatric

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. This behavior 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.

Suicidal Behavior and Ideation

There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behavior.

It is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behavior, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behavior should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen (see **ADVERSE REACTIONS**, Post-Marketing).

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants used to treat ADHD, such as APO-DEXTROAMPHETAMINE SR, 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.

Special Populations

Pregnant Women: Safe use in pregnancy has not been established. 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 manifested by dysphoria, agitation and significant lassitude. Reproductive studies in mammals at high multiples of the human dose have suggested an embryotoxic and a teratogenic potential. Use of amphetamines by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and child.

Nursing Women: Amphetamines are excreted in human milk. Mothers taking APO-DEXTROAMPHETAMINE SR should be advised to refrain from nursing. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age): Amphetamines are not recommended for use in Attention-Deficit Hyperactivity Disorder in children under 6 years of age, since safety and efficacy in this age group have not been established. Long-term effects of amphetamines in children above 6 years of age have not been well established (see also **WARNINGS AND PRECAUTIONS**, Long-term Suppression of Growth section).

Chronic administration of amphetamines may be associated with growth inhibition; growth should be monitored during treatment.

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

The presence of tics or Tourette's syndrome should be ruled out before administering amphetamines to children (see also **CONTRAINDICATIONS** section).

Geriatrics (> 65 years of age): The safety and efficacy of APO-DEXTROAMPHETAMINE SR in this patient population have not been established.

Renal Impairment: Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), dosage reduction should be considered in these patients.

As d-amphetamines are not dialyzable, dosage reduction may be considered in patients undergoing dialysis.

Monitoring and Laboratory Tests

Amphetamines can elevate plasma corticosteroid levels, particularly in the evening, and may interfere with urinary steroid determinations.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been

isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Overstimulation, restlessness, dizziness, euphoria or dysphoria, dyskinesia, headache, insomnia, exacerbation of motor and phonic tics, Tourette's syndrome, tremor; rarely, psychotic episodes at recommended doses.

Gastrointestinal: Dryness of the mouth, unpleasant taste, loss of appetite, diarrhea, constipation, other gastrointestinal disturbances, anorexia and weight loss.

Allergic: Urticaria.

Other: Impotence, changes in libido.

Post-Market Adverse Drug Reactions

The following unexpected serious adverse events have been reported in users of dextroamphetamine sulfate in the post-marketing period. These adverse events are compiled from spontaneous reports and are listed regardless of frequency and whether or not causal relationship with dextroamphetamine sulfate has been established.

Cardiovascular: atrial fibrillation, blood pressure abnormal, heart rate irregular, hypotension, myocardial infarction, sudden/cardiac death, thrombosis.

Central Nervous System: cerebrovascular accident, fall, hemorrhagic stroke, subdural hematoma

Endocrine Disorders: blood sugar fluctuation, blood glucose increased, hypoglycemia.

Gastro-intestinal: tooth disorder

General disorders and administration site conditions: condition aggravated, chest pain, drug ineffective, feeling abnormal, general physical health deterioration

Immune System Disorder: anaphylactic reaction

Investigation: prostatic specific antigen increased, sperm concentration zero

Neoplasm benign, malignant and unspecified: pancreatic neoplasm, prostate cancer

Neuromuscular and skeletal: muscle spasm

Psychiatric: screaming

Renal and urinary disorders: bladder disorder, incontinence, urinary incontinence

Skin: Livedo reticularis, skin discoloration

Suicidal Behavior and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see **WARNINGS AND PRECAUTIONS**, Suicidal Behavior and Ideation).

DRUG INTERACTIONS

Drug-Drug Interactions

Caution should be exercised when co-prescribing amphetamines and other drugs since clinically significant interactions with a number of drugs have been reported. In some instances, potentiation of CNS and cardiac effects could be life threatening. Dosages should be closely monitored.

Known interactions with amphetamines are as follows:

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 amphetamines.

Adrenergic Blockers
Adrenergic blockers are inhibited by amphetamines.

Alkalinizing Agents
Gastrointestinal alkalinizing agents (sodium bicarbonate, PPI, and other antacids) 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.

Tricyclic Antidepressants
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.

MAO Inhibitors
Concomitant treatment with MAO inhibitors or within 14 days following the withdrawal of MAO inhibitors is contraindicated. MAO Inhibitors, 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; 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 antagonize the hypotensive effects of antihypertensives (*e.g.* guanethidine).

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 effects of amphetamines.

Insulin
Amphetamines may alter insulin requirements in diabetes mellitus.

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.

Serotonergic Drugs
On rare occasions, serotonin syndrome has occurred in association with the use of amphetamines when given in conjunction with serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). As these syndromes may result in potentially life-threatening conditions (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma), treatment with serotonergic drugs should be discontinued if such events occur and supportive symptomatic treatment should be initiated. APO-DEXTROAMPHETAMINE SR should also be used with caution in combination with other drugs such as triptans, certain tricyclic antidepressants, certain opiate analgesics, lithium, St. John's Wort, tryptophan and MAO inhibitors due to the risk of serotonergic syndrome.

Veratrum Alkaloids
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug-Food Interactions

There are no known food interactions with dextroamphetamine sulfate.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels particularly in the evening, and thus may affect urinary steroid determinations.

DOSAGE AND ADMINISTRATION

Dosing Considerations

APO-DEXTROAMPHETAMINE SR should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted, to the lowest

effective dosage, since individual patient response to APO-DEXTROAMPHETAMINE SR varies widely. Time of administration should receive special attention because of possible insomnia. Late evening medication should be avoided.

APO-DEXTROAMPHETAMINE SR should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use stimulants or c) have a family history of sudden/cardiac death. Prior to the initiation of treatments, a personal and family history should be obtained. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered.

Patients who are considered to need extended treatment with APO-DEXTROAMPHETAMINE SR should undergo periodic evaluation of their cardiovascular status. (see **WARNINGS AND PRECAUTIONS**).

Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1.73 m^2), dosage reduction should be considered in these patients. As d-amphetamines are not dialyzable, dosage reduction may be considered in patients undergoing dialysis.

Recommended Dose and Dosage Adjustment

Adjunctive treatment of Narcolepsy:

Daily dosage may range from 5 mg to 60 mg depending on individual patient response.

- Suggested initial dosage for patients aged 6 to 12; start with 5 mg daily; daily dosage 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 optimal response is obtained.

If bothersome adverse reactions appear (*e.g.*, insomnia or anorexia), dosage should be reduced. Capsules may be used for once-a-day dosage wherever appropriate.

Attention-deficit Hyperactivity Disorder in children:

Daily dosage may range from 2.5 mg to 40 mg, although some older children may require more than 40 mg daily for optimal response. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Capsules may be used for once-a-day dosage wherever appropriate.

- Not recommended for this use in children under 6 years of age.
- In children 6 years of age or 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.

Most children suffering from Attention-Deficit Hyperactivity Disorder require medication for several years, although once symptoms have been controlled, it may be possible to reduce dosage or to interrupt drug therapy during the summer months and at other times when the child is under less stress. During periods of interrupted drug therapy, behavioral symptoms should be assessed to determine whether their recurrence is sufficient to justify the resumption of treatment.

Missed Dose

If forgotten, the medicine should be taken as soon as remembered and administration should continue as usual. Double dose should not be taken to make up for forgotten individual doses.

OVERDOSAGE

The toxic dose of amphetamine varies widely according to the degree of tolerance present. Blood levels are, therefore, of little value in assessing the severity of the overdose; this assessment must depend almost entirely on clinical signs.

Signs/Symptoms

Manifestations of acute overdosage include: Dilated and reactive pupils, shallow rapid respiration, rhabdomyolysis, hyperpyrexia, fever, chills, sweating, hyperactive tendon reflexes.

Other manifestations:

Central effects may include restlessness, tremor, aggressiveness, anxiety, confusion, delirium, hallucinations, panic attacks and even 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, diarrhea, abdominal cramps.

Fatal poisoning is usually preceded by convulsions and coma.

Treatment

Treatment is essentially symptomatic and supportive. In addition to the usual measures, including administration of activated charcoal (use of activated charcoal should be avoided in patients with significant risk of aspiration in whom the airway is not protected), emesis, gastric lavage and catharsis, sedatives should be given when indicated.

The prolonged release of APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate sustained-release capsules) should be considered when treating patients with overdose. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

Benzodiazepines are first-line agents in amphetamine overdose for agitation, movement disorders, seizures, tachycardia, and hypertension.

Second-line therapies may include antipsychotics such as chlorpromazine, ziprasidone or haloperidol. These drugs antagonize the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. However, caution should be excercised when administering these products as they may worsen clinical outcomes related to toxicity of co-ingestant, including other stimulants (e.g. cocaine) and ethanol withdrawal. Central alpha-2 adrenergic agonists, such as dexmedetomidine, are sometimes used for refractory amphetamine- induced agitation as they may have an additional advantage in that they can mitigate the tachycardia and hypertension often seen in these situations.

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. In the presence of severe hypotension, the usual procedures employed for shock should be instituted.

Seizures resistant to benzodiazepines may respond to barbiturates, or require escalation of care, including endotracheal intubation and initiation of propofol infusion.

Although previously advocated, enhancing amphetamine excretion via urine acidification is no longer recommended due to lack of effects on amphetamine toxicity and potential compromises in overall patient management (systemic acidosis, renal effects from rhabdomyolysis).

The d-amphetamines are not dialyzable. No data is available to support the recommendation of forced diuresis, hemodialysis, peritoneal dialysis or charcoal hemoperfusion in this regard.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dextroamphetamine (dexamphetamine, d-amphetamine) sulfate is a sympathomimetic agent. Like other amphetamines, dextroamphetamine substantially blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space. It has actions qualitatively similar to those of amphetamine sulfate but is approximately twice as potent. It has a marked stimulant effect on the central nervous system, particularly the cerebral cortex and the respiratory and vasomotor centers.

Dextroamphetamine sulfate causes a lessening of fatigue, an increase in mental activity, an elevation of mood, and a general feeling of well-being. However, its indiscriminate use in attempts to increase capacity for work or to overcome fatigue is undesirable. At high doses, it produces a euphoria, which upon abrupt withdrawal of the drug reverts to severe depression and lethargy.

The mechanism by which amphetamines produce mental and behavioral effects in children is not conclusively established.

Metabolism

Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved. As CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

STORAGE AND STABILITY

Keep out of the reach and sight of children. APO-DEXTROAMPHETAMINE SR should be stored at 15°C -30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 10 mg and 15 mg capsules:

Each sustained release capsule contains the medicinal ingredient dextroamphetamine sulfate (10 mg or 15 mg) and releases a therapeutic dose promptly with the remaining dose being delivered gradually without interruption to sustain the effects for 10 to 12

hours.

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 10 mg:

APO-DEXTROAMPHETAMINE SR 10 mg capsule is a hard gelatin capsule with medium orange opaque body and black opaque cap, imprinted APO D10 in white ink and filled with white to off-white round, biconvex tablets. Inactive ingredients consist of Colloidal silicon dioxide, ethylcellulose, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6, gelatin, hydroxypropyl cellulose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide.

Available in HDPE bottles of 100 and 500 capsules.

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 15 mg:

APO-DEXTROAMPHETAMINE SR 15 mg capsule is a hard gelatin capsule with medium orange opaque body and black opaque cap, imprinted APO D15 in white ink and filled with white to off-white round, biconvex tablets. Inactive ingredients consist of Colloidal silicon dioxide, ethylcellulose, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6, gelatin, hydroxypropyl cellulose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide.

Available in HDPE bottles of 100 and 500 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

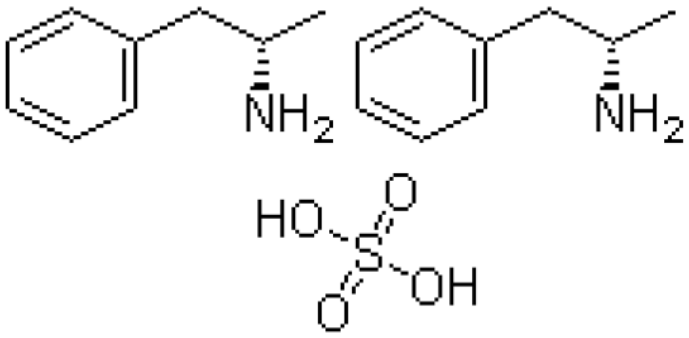
Proper name: dextroamphetamine sulfate

Chemical name: (+)-α-Methylphenethylamine hemisulfate salt

Molecular formula: $2(C_9H_{13}N)\cdot H_2SO_4$

Molecular mass: 368.49 g/mol

Structural formula:



CLINICAL TRIALS

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male and female volunteers. The results obtained from 23 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of dextroamphetamine was measured and compared following a single oral dose (1 x 15 mg sustained release capsule) of APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 15 mg Sustained Release Capsules (Apotex Inc.) and DEXEDRINE® SPANSULE® (dextroamphetamine sulfate) 15 mg Capsules (Paladin Labs Inc.).

Dextroamphetamine (1 x 15 mg) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUCt (ng•h/mL)	647.4 669.7 (26.6)	677.3 697.0 (23.3)	95.6	91.5 – 99.8
AUC_{inf} (ng•h/mL)	674.9 701.9 (29.0)	700.8 722.4 (24.0)	96.3	92.0 – 100.8
C_{max} (ng/mL)	23.5 24.1 (24.2)	26.5 27.0 (20.9)	88.6	85.0 – 92.5
T_{max}[§] (h)	8.25 (34.26)	7.48 (17.49)		
$T_{1/2}$[§] (h)	11.28 (23.43)	10.95 (14.61)		

* APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 15 mg Sustained Release Capsules (Apotex Inc.)

† DEXEDRINE® SPANSULE® (dextroamphetamine sulfate) 15 mg Capsules (Paladin Labs Inc.) was purchased in Canada.

Based on Geometric Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male and female volunteers. The results obtained from 23 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of dextroamphetamine was measured and compared following a single oral dose (1 x 15 mg sustained release capsule) of APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 15 mg Sustained Release Capsules (Apotex Inc.) and DEXEDRINE® SPANSULE® (dextroamphetamine sulfate) 15 mg Capsules (Paladin Labs Inc.).

Dextroamphetamine (1 x 15 mg) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUCt (ng•h/mL)	584.0 595.1 (18.3)	599.7 616.0 (22.9)	97.4	93.7 – 101.2
AUCinf (ng•h/mL)	617.1 629.5 (19.4)	621.0 639.3 (23.9)	99.4	95.7 – 103.2
C_{max} (ng/mL)	22.1 22.4 (16.2)	26.8 27.3 (18.3)	82.4	78.8 – 86.1
T_{max}[§] (h)	7.76 (37.45)	5.96 (28.41)		
$T_{1/2}$[§] (h)	12.71 (24.33)	11.51 (19.59)		

* APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate) 15 mg Sustained Release Capsules (Apotex Inc.)

† DEXEDRINE® SPANSULE® (dextroamphetamine sulfate) 15 mg Capsules (Paladin Labs Inc.) was purchased in Canada.

Based on Geometric Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

TOXICOLOGY

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d,l*-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

REFERENCES

Product Monograph DEXEDRINE® SPANSULE®, Paladin Labs Inc., Control No. 183401, Date of Revision: March 21, 2016, Version 9.0

PART III: CONSUMER INFORMATION

APO-DEXTROAMPHETAMINE SR
Dextroamphetamine sulfate sustained release capsules
10 mg and 15 mg

Apotex Standard

This leaflet is part III of a three-part "Product Monograph" published when APO-DEXTROAMPHETAMINE SR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-DEXTROAMPHETAMINE SR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

APO-DEXTROAMPHETAMINE SR (dextroamphetamine sulfate), a drug in the class of amphetamines (central nervous system stimulant), is used along with other therapies, for the treatment of:

- narcolepsy (a disorder that caused excessive sleepiness during the day and frequent and uncontrollable episodes of falling asleep).
- Attention-deficit Hyperactivity Disorder (ADHD) (a disorder characterized by a very short attention span, impulsiveness, and hyperactivity). APO-DEXTROAMPHETAMINE SR should be used as a part of a total treatment program for ADHD that may include counselling or other therapies.

What it does:

APO-DEXTROAMPHETAMINE SR causes a lessening of fatigue, an increase in mental activity, an elevation of mood, and a general feeling of well-being.

APO-DEXTROAMPHETAMINE SR helps increase attention (including the ability to follow directions and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD.

When it should not be used:

You or your child should NOT take APO-DEXTROAMPHETAMINE SR if you or your child:

- have cardiovascular disease;
- have moderate to severe high blood pressure;
- have advanced arteriosclerosis (hardened arteries);
- have hyperthyroidism (an overactive thyroid gland);
- have allergies to APO-DEXTROAMPHETAMINE SR or to any ingredient in the formulation or component of the container;
- are sensitive to, allergic to, or had a reaction to other stimulant medicines or sympathomimetic amines;
- have glaucoma, an eye disease;
- have very anxious, tense, or agitated states;
- have motor tics (hard to control, repeat twitching of any parts of the body) or verbal tics (hard to control repeating of sounds or words) or Tourette's syndrome;
- have relatives with motor tics or verbal tics or Tourette's syndrome;
- are taking drugs from the group called Monoamine Oxidase Inhibitors (MAOI) or have taken a MAOI within the last 14 days;
- have a history of drug abuse.

APO-DEXTROAMPHETAMINE SR is not recommended for use in children under 6 years of age.

Talk to your doctor if you believe any of these conditions apply to you or your child.

What the medicinal ingredient is:

APO-DEXTROAMPHETAMINE SR contains dextroamphetamine sulfate as the medicinal ingredient.

What the nonmedicinal ingredients are:

APO-DEXTROAMPHETAMINE SR 10 mg and 15 mg contain the following non-medicinal ingredients: Colloidal silicon dioxide, ethylcellulose, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6, gelatin, hydroxypropyl cellulose, iron oxide red, iron oxide yellow, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide.

What dosage forms it comes in:

APO-DEXTROAMPHETAMINE SR is available as 10 mg and 15 mg capsules.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Dependence**
  Abuse of any amphetamine like APO-DEXTROAMPHETAMINE SR can lead to dependence. Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

The following have been reported with use of APO-DEXTROAMPHETAMINE SR and other medicines used to treat ADHD:

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

Sudden death has been reported in association with stimulant drugs for ADHD treatment in children with structural heart abnormalities. APO-DEXTROAMPHETAMINE SR generally should not be used in children, adolescents or adults with known structural heart abnormalities.

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 may wish to check you or your child carefully for heart problems before starting APO-DEXTROAMPHETAMINE SR.

Your doctor may wish to check you or your child's blood pressure and heart rate regularly during treatment with APO-DEXTROAMPHETAMINE SR.

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 APO-DEXTROAMPHETAMINE SR.

2. <u>Mental (Psychiatric) problems:</u>

All patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**
- **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 APO-DEXTROAMPHETAMINE SR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

Amphetamines may impair the ability to perform potentially hazardous activities such as operating machinery or driving.

BEFORE you use APO-DEXTROAMPHETAMINE SR talk to your doctor or pharmacist if you or your child:

- have mild high blood pressure;
- have a family history of sudden death or death related to heart problems;
- have heart disease or structural heart abnormalities;
- have mental problems including psychosis, mania, bipolar illness, depression, or a family history of suicide;
- have tics or Tourette's syndrome;
- have thyroid problems;
- have seizures or have had an abnormal brain wave test (EEG);
- do strenuous exercise;
- take other drugs for ADHD;
- have diabetes mellitus;
- have kidney disease
- have an allergy to aspirin;
- is pregnant or plans to become pregnant;
- is breast feeding or plans to breastfeed;
- if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.
- Have circulation problems in fingers and toes, including numbness, feeling cold or pain (this is also known as Raynaud's phenomenon.).

Amphetamines have been subject to extensive abuse. Tolerance, extreme psychological dependence, and severe social disability can occur. It is important that APO-DEXTROAMPHETAMINE SR be taken only as directed by your doctor.

INTERACTIONS WITH THIS MEDICATION

It is important to tell your doctor or pharmacist about all medicines that you or your child are taking including other medicines that a doctor has prescribed, medicines that you buy yourself without a prescription, and any herbal remedies that you or your child are taking, especially:

- medicines that make urine or digestive contents more acidic (e.g., guanethidine, reserpine, ascorbic acid, ammonium chloride, sodium acid phosphate)
- medicines that make urine or digestive contents more alkaline (e.g., sodium bicarbonate, acetazolamide, thiazides)
- medicines used to treat depression including monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and certain tricyclic antidepressants (TCAs)
- Other medicines that can affect serotonin, such as lithium, drugs containing tryptophan,St. John's Wort, triptans used to treat migraines and certain medicines used to treat pain, such as fentanyl, tramadol, tapentadol, meperidine, methadone
- Medicines used to reduce your blood pressure (such as guanethidine and veratrum alkaloids)
- Medicines used to treat allergy symptoms (antihistamines)
- Antipsychotic medicines (such as chlorpromazine and haloperidol)
- Insulin (a drug used to treat diabetes)
- Lithium carbonate (a drug used to treat bipolar disorder)
- Medicines used to treat pain (such as meperidine and propoxyphene)
- Norepinephrine
- Phenobarbital (a drug used to help you fall asleep or treat anxiety)
- Antacids such as Proton Pump Inhibitors
- Seizure medicines (such as ethosuximide, phenytoin)

While on APO-DEXTROAMPHETAMINE SR do not start taking a new medicine or herbal remedy before checking with your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:

In order to receive the most benefit from APO-DEXTROAMPHETAMINE SR, it is important that APO-DEXTROAMPHETAMINE SR be taken only as directed by your doctor. The doctor may adjust the amount of drug taken by you or your child until it is right for you or your child. From time to time, the doctor may interrupt treatment to check you or your child's symptoms while you or your child are not taking the drug.

Your doctor may do regular checks of the blood, heart, and blood pressure while taking APO-DEXTROAMPHETAMINE SR. Children should have their height and weight checked often while taking APO-DEXTROAMPHETAMINE SR treatment may be stopped if a problem is found during these check-ups.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your medicine, take it as soon as you remember. Then continue as before. Do not take a double dose to make up for forgotten individual doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its desired effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, talk to your or your child's doctor.

Some of the side effects observed during treatment with stimulant medications such as APO-DEXTROAMPHETAMINE SR were slowing of growth (height and weight) in children, seizures (mainly in patients with a history of seizures), eye sight changes, tremors, headache, dizziness, loss of appetite, dry mouth, stomach upset, difficulty falling asleep, high blood pressure, irregular heartbeat, and irritability.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Seek immediate medical help
		Only if severe	In all cases	
Common	**Uneven heartbeat (palpitations)**		✓	
	Slowing of growth (height and weight) in children		✓	
	Anxiety	✓		
	New tics		✓	
Uncommon	**Allergic Reaction**: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Trouble with vision: eyesight changes and blurred visions		✓	
	New Psychotic or Manic Symptoms: – Paranoia, delusions – Hallucinations: seeing, feeling, or hearing things that are not real – Mania: feeling unusually excited, over-active, or uninhibited		✓	
	Aggressive Behavior or Hostility		✓	
	Depression: feeling sad, loss of interest in usual activities,		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Seek immediate medical help
		Only if severe	In all cases	
	hopelessness, insomnia, or sleeping too much			
Unknown rate	**Fits (seizures)**			✓
	Suicidal Behavior: Thoughts or actions about hurting or killing yourself			✓
	Cardiomyopathy: breathlessness or swelling of the legs (signs of heart muscle disease)		✓	
	Raynaud's Phenomenon: discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	

This is not a complete list of side effects. For any unexpected effects while taking APO-DEXTROAMPHETAMINE SR, contact your doctor or pharmacist.

HOW TO STORE IT

APO-DEXTROAMPHETAMINE SR capsules should be stored at 15°C-30°C.

Do not take your medicine after the expiry date shown on the bottle.

Keep this medicine out of the reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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