ADDERALL® CII **Rx ONLY**

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

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

DESCRIPTION:

A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate monohydrate.

EACH TABLET CONTAINS:	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	4.7 mg	6.3 mg	7.8 mg	9.4 mg	12.6 mg	18.8 mg

Inactive Ingredients: lactitol, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate, and other ingredients.

Colors: ADDERALL® 5 mg is a white to off-white tablet, which contains no color additives.
ADDERALL® 7.5 mg and 10 mg contain FD & C Blue #1.
ADDERALL® 12.5 mg, 15 mg, 20 mg and 30 mg contain FD & C Yellow #6 as a color additive.

CLINICAL PHARMACOLOGY:

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

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

Pharmacokinetics

ADDERALL® tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30 mg of ADDERALL® to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-amphetamine. The mean elimination half-life ($t_{1/2}$) for d-amphetamine was shorter than the $t_{1/2}$ of the l-isomer (9.77-11 hours vs. 11.5-13.8 hours). The PK parameters (C_{max}, $AUC_{0\text{-}inf}$) of d-and l-amphetamine increased approximately three-fold from 10 mg to 30 mg indicating dose-proportional pharmacokinetics.

The effect of food on the bioavailability of ADDERALL® has not been studied.

INDICATIONS:
Attention Deficit Disorder with Hyperactivity: ADDERALL® is 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 with 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.

In Narcolepsy

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

Patients with a history of drug abuse.

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

WARNINGS:
Psychosis: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall generally should not be used in children or adults with structural cardiac abnormalities.

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

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

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Blood pressure and pulse should be monitored at appropriate intervals in patients taking Adderall, especially patients with hypertension.

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

Drug Interactions: *Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.
Urinary acidifying agents -(ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blocker -Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents -Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
MAO inhibitors -MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -Amphetamines may counteract the sedative effect of antihistamines.
Antihypertensives -Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -Chlorpromazine blocks dopamine and norepinephrine receptors, 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 receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:
- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

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

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

Pediatric Use: Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

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.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines 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 amphetamines is usually not indicated.

ADVERSE REACTIONS:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

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

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE:

Dextroamphetamine Sulfate, Amphetamine Sulfate, Amphetamine Aspartate Monohydrate, and Dextroamphetamine Saccharate are Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times than 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 amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

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

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

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

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

DOSAGE AND ADMINISTRATION:
Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it

be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

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

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

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

HOW SUPPLIED:
ADDERALL® 5 mg: A round, flat-faced beveled edge, white to off-white tablet, “5” embossed on one side with partial bisect and “AD” embossed on the other side (NDC 54092-371-01)

ADDERALL® 7.5 mg: An oval, convex, blue tablet, “7.5” embossed on one side with a partial bisect and “AD” embossed on the other side with a full and partial bisect (NDC 54092-372-01)

ADDERALL® 10 mg: A round, convex, blue tablet, “10” embossed on one side with a full and partial bisect and “AD” embossed on the other side (NDC 54092-373-01)

ADDERALL® 12.5 mg: A round, flat-faced beveled edge, orange tablet, “12.5” embossed on one side and “AD” embossed on the other side with a full and partial bisect (NDC 54092-374-01)

ADDERALL® 15 mg: An oval, convex, orange tablet, “15” embossed on one side with a partial bisect and “AD” embossed on the other side with a full and partial bisect (NDC 54092-375-01)

ADDERALL® 20 mg: A round, convex, orange tablet, “20” embossed on one side with a full and partial bisect and “AD” embossed on the other side (NDC 54092-376-01)

ADDERALL® 30 mg: A round, flat-faced beveled edge, orange tablet, “30” embossed on one side with a full and partial bisect and “AD” embossed on the other side (NDC 54092-377-01)

In bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25°C (77°F), excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]

Rx only.

MG #001765 Revised: 06/05
371 0107 004

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

DESCRIPTION

ADDERALL XR® is a once daily extended-release, single-entity amphetamine product. ADDERALL XR® combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The ADDERALL XR® capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from ADDERALL XR® compared to the conventional ADDERALL® (immediate-release) tablet formulation.

EACH CAPSULE CONTAINS:	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in ADDERALL XR® capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR® have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and adolescent (13-17 yrs) and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and ADDERALL XR® capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR® is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

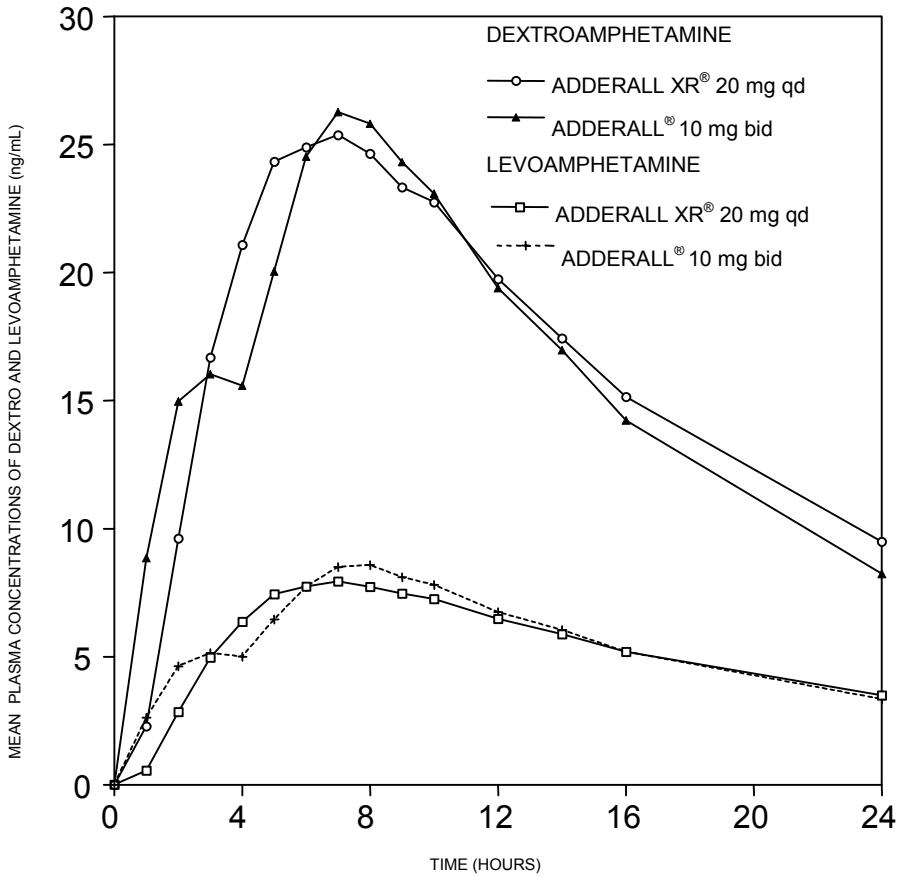

Figure 1 Mean d-amphetamine and l-amphetamine plasma concentrations following administration of ADDERALL XR® 20 mg (8am) and ADDERALL® (immediate-release) 10 mg bid (8am and 12 noon) in the fed state.

A single dose of ADDERALL XR® 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-live for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13-17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis children have a higher clearance than adolescents or adults (See Special Populations).

ADDERALL XR® demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents weighing greater than 75 kg/165lbs, and over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l-amphetamine after administration of ADDERALL XR® 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR® strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively.

Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased, (See PRECAUTIONS).

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR® in pediatric (6-12 years) and adolescent (13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_∞) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR®, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Clinical Trials

Children

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6-12 (N=584) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg of ADDERALL XR® or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR® doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR® subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR® showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg ADDERALL XR® demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

Adolescents

A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 (N=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤ 75kg/165lbs) was randomized to fixed dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg ADDERALL XR® or placebo once daily in the morning; patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75kg/165lbs who were randomized to fixed dose treatment groups receiving final doses of 50 mg and 60 mg ADDERALL XR® or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the ADHD-RS-IV total scores for the primary cohort. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR® 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adults

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of ADDERALL XR® or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD, were observed at endpoint for all ADDERALL XR® doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two 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 six 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 six 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. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome 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 child and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program: ADDERALL XR® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of ADDERALL XR® for long-term use, i.e., for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Agitated states.

Patients with a history of drug abuse.

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

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children, adolescents, or adults with structural cardiac abnormalities.

PRECAUTIONS

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

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.

Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication.

In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR® 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥ 8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR®-treated patients. Similar results were observed at higher doses.

In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR®, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

Tics: 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.

Effects on Weight: Amphetamines have been associated with decreased appetite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These reductions in expected weight attenuate over time and are greatest in the heaviest children. In the controlled trial in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg ADDERALL XR®. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

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

Drug Interactions: *Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.
Urinary acidifying agents -These 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, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -Amphetamines may enhance the activity of tricyclic antidepressants 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 -MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -Amphetamines may counteract the sedative effect of antihistamines.
Antihypertensives -Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -Chlorpromazine blocks dopamine and norepinephrine receptors, 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 receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

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

Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m ^{2} body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

Pregnancy: Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

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.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

Pediatric Use: ADDERALL XR® is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: ADDERALL XR® has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR® included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N= 40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and,

0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, respectively, treated with ADDERALL XR® or placebo are presented in the tables below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or more of Adolescents Weighing ≤ 75 kg/165 lbs Receiving ADDERALL XR® with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite [b]	36%	2%
Nervous System	Insomnia [b]	12%	4%
	Nervousness	6%	6%[a]
Metabolic/Nutritional	Weight Loss [b]	9%	0%

[a] Appears the same due to rounding

[b] Dose-related adverse events

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

*Included doses up to 40 mg

Table 3 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 3 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*Included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

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

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR® is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states,
hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

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

The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the therapeutic needs and response of the patient. ADDERALL XR® should be administered at the lowest effective dosage.

Children

In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children is 30 mg/day; doses greater than 30 mg/day of ADDERALL XR® have not been studied in children. Amphetamines are not recommended for children under 3 years of age. ADDERALL XR® has not been studied in children under 6 years of age.

Adolescents

The recommended starting dose for adolescents who are 13-17 years of age with ADHD is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

Patients Currently Using ADDERALL®- Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL®, for example twice a day, may be switched to ADDERALL XR® at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

ADDERALL XR® capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

ADDERALL XR® may be taken with or without food.

ADDERALL XR® should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

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:
ADDERALL XR® 5 mg Capsules: Clear/blue (imprinted ADDERALL XR 5 mg), bottles of 100, NDC 54092-381-01
ADDERALL XR® 10 mg Capsules: Blue/blue (imprinted ADDERALL XR 10 mg), bottles of 100, NDC 54092-383-01
ADDERALL XR® 15 mg Capsules: Blue/white (imprinted ADDERALL XR 15 mg), bottles of 100, NDC 54092-385-01
ADDERALL XR® 20 mg Capsules: Orange/orange (imprinted ADDERALL XR 20 mg), bottles of 100, NDC 54092-387-01
ADDERALL XR® 25 mg Capsules: Orange/white (imprinted ADDERALL XR 25 mg), bottles of 100, NDC 54092-389-01
ADDERALL XR® 30 mg Capsules: Natural/orange (imprinted ADDERALL XR 30 mg), bottles of 100, NDC 54092-391-01

Dispense in a tight, light-resistant container as defined in the USP.
Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

ANIMAL TOXICOLOGY
Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

Manufactured for Shire US Inc., Wayne, PA 19087. Made in USA.

For more information call 1-800-828-2088 or visit www.adderallxr.com

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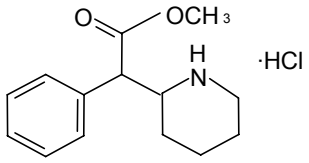
CONCERTA® (methylphenidate HCl)
Extended-release Tablets CII

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the

drug concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that CONCERTA® extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 to 10 hours.

CONCERTA® qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid (see Figure 1). The relative bioavailability of CONCERTA® qd and methylphenidate tid in adults is comparable.

FIGURE 1

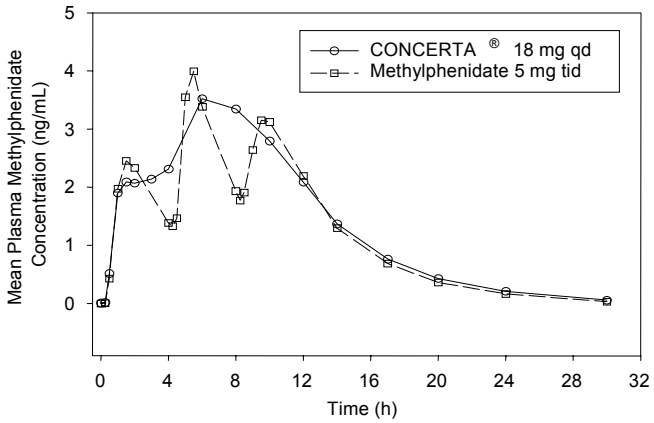


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA® 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.

TABLE 1
Mean ± SD Pharmacokinetic Parameters

Parameters	CONCERTA® (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of CONCERTA® 18 mg.

Dose Proportionality

Following administration of CONCERTA® in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC $_{(0\text{-inf})}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and AUC $_{(0\text{-inf})}$ increased disproportionately with respect to dose.

Following administration of CONCERTA®, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of CONCERTA®, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to α-phenyl-piperidine acetic acid (PPA), which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated once-daily doses of CONCERTA® is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-inf})}$ values for CONCERTA® were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA®, dose-adjusted $AUC_{(0\text{-inf})}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age
Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of CONCERTA® has not been studied in children less than 6 years of age.

Renal Insufficiency
There is no experience with the use of CONCERTA® in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA®.

Hepatic Insufficiency
There is no experience with the use of CONCERTA® in patients with hepatic insufficiency.

Clinical Studies
CONCERTA was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Children
Three double blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12. The controlled studies compared CONCERTA® given qd (18, 36, or 54 mg), methylphenidate given tid over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention / Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention / Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA®. The scores for CONCERTA® and placebo for the three studies are presented in Figure 2.

FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners
Inattention/Overactivity Scores

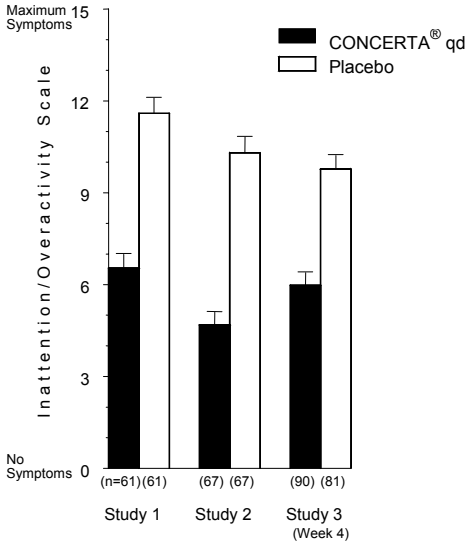
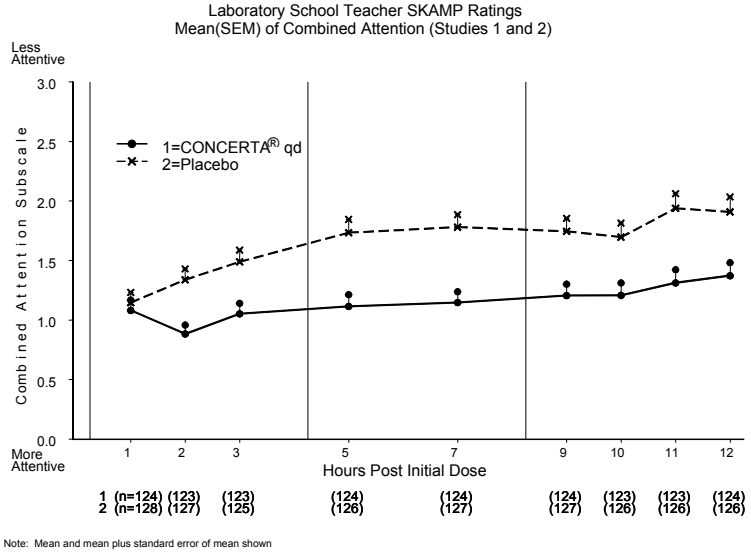


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® once-daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for CONCERTA® and placebo.
*Swanson, Kotkin, Agler, M-Fynn and Pelham

FIGURE 3



Note: Mean and mean plus standard error of mean shown

Adolescents

In a randomized, double blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of CONCERTA® (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that CONCERTA® was significantly superior to placebo

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of CONCERTA® in the treatment of ADHD was established in three controlled trials of children aged 6-12 and in one controlled trial in adolescents aged 13-17. All patients met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, eg, in social, academic, or occupational functioning, and be present in two or more settings, eg, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six 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 six 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. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and 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

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

Long-Term Use

The effectiveness of CONCERTA® for long-term use, ie, for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use CONCERTA® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) (see PRECAUTIONS, Drug Interactions).

WARNINGS

Depression

CONCERTA® should not be used to treat severe depression.

Fatigue

CONCERTA® should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

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

Seizures

There is some clinical evidence that methylphenidate 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 absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Hypertension and other Cardiovascular Conditions

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension.

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.

In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

Visual Disturbance
Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age
CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE
CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS
Hematologic Monitoring
Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients
Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patient information is printed at the end of this insert. To assure safe and effective use of CONCERTA®, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions
CONCERTA® should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).
Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an

in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

Pediatric Use

The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54 and/or 72 mg/day. Children, adolescents, and adults

with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA®

Adverse Events Associated with Discontinuation of Treatment

In the 4-week placebo-controlled, parallel-group trial in children (Study 3) one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).

In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA®) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients

Table 2 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in

1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2
Incidence of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® In Children

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 3 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

Table 3
Incidence of Treatment-Emergent Events[1] in a 2-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body System	Preferred Term	CONCERTA (n=87)	Placebo (n=90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Post-Marketing Experience with CONCERTA®:

Additional very rare undesirable effects were reported during the marketing experience: difficulties in visual accommodation, blurred vision, abnormal liver function test (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported.

Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: hepatic coma; isolated cases of cerebral arteritis and/or occlusion; anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdosage has not been established.

The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

DOSAGE AND ADMINISTRATION

CONCERTA® should be administered orally once daily in the morning with or without food as it has been shown to improve attention and behavior through 12 hours after dosing.

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS: Information for Patients).

Based on an assessment of clinical benefit and tolerability, doses may be increased at weekly intervals for patients who have not achieved an optimal response at a lower dose.

Patients New to Methylphenidate

The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patient Age	Recommended Starting Dose	Maximum Dosage
Children 6-12 years of age	18 mg/day	54 mg/day
Adolescents 13-17 years of age	18 mg/day	72 mg/day not to exceed 2 mg/kg/day

Patients Currently Using Methylphenidate

The recommended dose of CONCERTA® for patients who are currently taking methylphenidate bid or tid, at doses of 10 to 45 mg/day is provided in Table 4. Dosing recommendations are based on current dose regimen and clinical judgment. Initial conversion dosage should not exceed 54 mg daily. After conversion, dosages may be adjusted to a maximum of 72 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

TABLE 4
Recommended Dose Conversion from
Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dose
5 mg Methylphenidate bid or tid	18 mg q am
10 mg Methylphenidate bid or tid	36 mg q am
15 mg Methylphenidate bid or tid	54 mg q am

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

Nevertheless, the physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED

CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg 100 count bottle	NDC 17314-5850-2
27 mg 100 count bottle	NDC 17314-5853-2
36 mg 100 count bottle	NDC 17314-5851-2
54 mg 100 count bottle	NDC 17314-5852-2

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by
ALZA Corporation, Mountain View, CA 94043.
Distributed and Marketed by
McNeil Consumer & Specialty Pharmaceuticals
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INFORMATION FOR PATIENTS TAKING CONCERTA® OR THEIR PARENTS OR CAREGIVERS

CONCERTA® (methylphenidate HCl) Extended-release Tablets CII

This information is for patients taking CONCERTA® Extended-release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking CONCERTA®. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA®, talk to your doctor or pharmacist.

What is CONCERTA®?

CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA® work?

Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released with an increasing rate during the day to continue to help lessen the symptoms of ADHD Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA®?

You should NOT take CONCERTA® if:

- You have significant anxiety, tension, or agitation since CONCERTA® may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

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

How should I take CONCERTA®?

Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.

You may take CONCERTA® before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?

In the clinical studies with patients using CONCERTA®, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in CONCERTA®, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?

Talk to your doctor ***before*** taking CONCERTA® if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.

- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor immediately if you develop any of the above conditions or symptoms while taking CONCERTA®.

Can I take CONCERTA® with other medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take CONCERTA® with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take CONCERTA® with monoamine oxidase (MAO) inhibitors.

While on CONCERTA®, do not start taking a new medicine or herbal remedy before checking with your doctor.

CONCERTA® may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called “blood thinners”). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA®.

Other Important Safety Information

Abuse of methylphenidate 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.

Before taking CONCERTA®, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking CONCERTA®.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your CONCERTA® treatment.

Call your doctor ***immediately*** if you take more than the amount of CONCERTA® prescribed by your doctor.

What else should I know about CONCERTA®?

CONCERTA® has not been studied in children under 6 years of age.

The CONCERTA® tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

CONCERTA® may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA® with anyone else and take only the number of CONCERTA® tablets prescribed by your doctor.

CONCERTA® should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by
ALZA Corporation, Mountain View, CA 94043
Distributed and Marketed by
McNeil Consumer & Specialty Pharmaceuticals
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PRESCRIBING INFORMATION

Ⓒ II

DEXEDRINE®

(dextroamphetamine sulfate)
SPANSULE® sustained-release capsules and Tablets

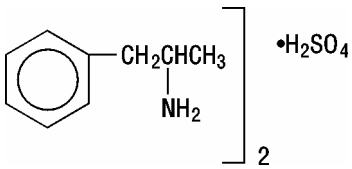
WARNING

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

DESCRIPTION

DEXEDRINE (dextroamphetamine sulfate) is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is *d*-alpha-methylphenethylamine, and is present in all forms of DEXEDRINE as the neutral sulfate.

Structural formula:



SPANSULE capsules: Each SPANSULE sustained-release capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period.

Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10-mg capsule is imprinted 10 mg—3513—on the brown cap and is imprinted 10 mg—SB—on the clear body. The 15-mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Product reformulation in 1996 has caused a minor change in the color of the time-released pellets within each capsule. Inactive ingredients now consist of cetyl alcohol, D&C Yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C Blue No. 1, FD&C Blue No. 1 aluminum lake, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hypromellose, propylene glycol,

povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.

Tablets: Each triangular, orange, scored tablet is debossed SKF and E19 and contains dextroamphetamine sulfate, 5 mg. Inactive ingredients consist of calcium sulfate, FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6, gelatin, lactose, mineral oil, starch, stearic acid, sucrose, talc, and trace amounts of other inactive ingredients.

CLINICAL PHARMACOLOGY

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

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

DEXEDRINE SPANSULE capsules are formulated to release the active drug substance in vivo in a more gradual fashion than the standard formulation, as demonstrated by blood levels. The formulation has not been shown superior in effectiveness over the same dosage of the standard, noncontrolled-release formulations given in divided doses.

Pharmacokinetics: The pharmacokinetics of the tablet and sustained-release capsule were compared in 12 healthy subjects. The extent of bioavailability of the sustained-release capsule was similar compared to the immediate-release tablet. Following administration of three 5-mg tablets, average maximal dextroamphetamine plasma concentrations (C_{max}) of 36.6 ng/mL were achieved at approximately 3 hours. Following administration of one 15-mg sustained-release capsule, maximal dextroamphetamine plasma concentrations were obtained approximately 8 hours after dosing. The average C_{max} was 23.5 ng/mL. The average plasma $T_{½}$ was similar for both the tablet and sustained-release capsule and was approximately 12 hours.

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

INDICATIONS AND USAGE

DEXEDRINE is indicated in:

Narcolepsy

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

abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

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

Agitated states.

Patients with a history of drug abuse.

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

PRECAUTIONS

General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at 1 time in order to minimize the possibility of overdosage.

The tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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

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

Adrenergic blockers: Adrenergic blockers are inhibited by amphetamines.

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

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

MAO inhibitors: MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the

release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines:Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives:Amphetamines may antagonize the hypotensive effects of antihypertensives.

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

Ethosuximide: Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

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

Meperidine: Amphetamines potentiate the analgesic effect of meperidine.

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

Norepinephrine: Amphetamines enhance the adrenergic effect of norepinephrine.

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

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

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

Veratrum alkaloids: Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.

Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of DEXEDRINE have not been performed.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. DEXEDRINE has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been 1 report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. DEXEDRINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Dextroamphetamine sulfate is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the

dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.

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

OVERDOSAGE

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

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

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, assaultiveness, hallucinations, panic states.

Fatigue and depression usually follow the central stimulation.

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

TREATMENT

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

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

Since much of the SPANSULE capsule medication is coated for gradual release, therapy directed at reversing the effects of the ingested drug and at supporting the patient should be continued for as long as overdosage symptoms remain. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

DOSAGE AND ADMINISTRATION

Amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses—particularly with the SPANSULE capsule form—should be avoided because of the resulting insomnia.

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

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

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

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

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

SPANSULE capsules may be used for once-a-day dosage wherever appropriate.

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

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

HOW SUPPLIED

DEXEDRINE SPANSULE capsules: Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10-mg capsule is imprinted 10 mg—3513—on the brown cap and is imprinted 10 mg—SB—on the clear body. The 15-mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Available: 5 mg, 10 mg, and 15 mg in bottles of 100.

Store at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP].

Dispense in a tight, light-resistant container.

5 mg 100s: NDC 0007-3512-20

10 mg 100s: NDC 0007-3513-20

15 mg 100s: NDC 0007-3514-20

DEXEDRINE Tablets: Triangular, orange, scored, debossed SKF and E19. Available: 5 mg in bottles of 100.

Store between 15° and 30°C (59° and 86°F). Dispense in a tight, light-resistant container.

5 mg 100s: NDC 0007-3519-20

Manufactured by
Cardinal Health
Winchester, KY 40391
for **GlaxoSmithKline**
Research Triangle Park, NC 27709

October 2005

DX:L54

NOVARTIS

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89015703

Ritalin LA®

(methylphenidate hydrochloride)
extended-release capsules

Rx only

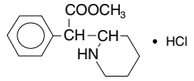
Prescribing Information

DESCRIPTION

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant.

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules is an extended-release formulation of methylphenidate with a bimodal release profile. Ritalin LA® uses the proprietary SODAS™ (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Ritalin LA capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate. Ritalin LA 10, 20, 30, and 40 mg capsules provide in a single dose the same amount of methylphenidate as dosages of 5, 10, 15, or 20 mg of Ritalin® tablets given b.i.d.

The active substance in Ritalin LA is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive ingredients: ammonio methacrylate copolymer, black iron oxide (10 and 40 mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10 and 40 mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10, 30, and 40 mg capsules only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate hydrochloride, the active ingredient in Ritalin LA® (methylphenidate hydrochloride) extended-release capsules, is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d-* and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

Pharmacokinetics

Absorption

Ritalin LA produces a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately four hours apart) when orally administered to children diagnosed with ADHD and to healthy adults. The initial rate of absorption for Ritalin LA is similar to that of Ritalin tablets as shown by the similar rate parameters between the two formulations, i.e., initial lag time (T_{lag}), first peak concentration (C_{max1}), and time to the first peak (T_{max1}), which is reached in 1-3 hours. The mean time to the interpeak minimum (T_{minip}), and time to the second peak (T_{max2}) are also similar for Ritalin LA given once daily and Ritalin tablets given in two doses 4 hours apart (see Figure 1 and Table 1), although the ranges observed are greater for Ritalin LA.

Ritalin LA given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than Ritalin tablets given in two doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads (see Figure 1 and Table 1).

The relative bioavailability of Ritalin LA given once daily is comparable to the same total dose of Ritalin tablets given in two doses 4 hours apart in both children and in adults.

Figure 1. Mean plasma concentration time-profile of methylphenidate after a single dose of Ritalin LA® 40 mg q.d. and Ritalin® 20 mg given in two doses four hours apart

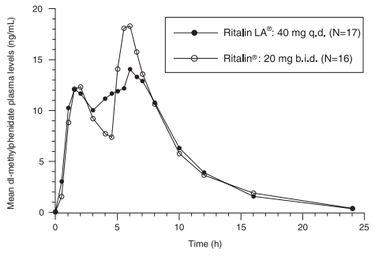


Table 1. Mean ± SD and range of pharmacokinetic parameters of methylphenidate after a single dose of Ritalin LA® and Ritalin® given in two doses 4 hours apart

Population	Children		Adult Males	
Formulation	Ritalin®	Ritalin LA®	Ritalin®	Ritalin LA®
Dose	10 mg & 10 mg	20 mg	10 mg & 10 mg	20 mg
N	21	18	9	8
T_{lag} (h)	0.24 ± 0.44	0.28 ± 0.46	1.0 ± 0.5	0.7 ± 0.2
	0 - 1	0 - 1	0.7 - 1.3	0.3 - 1.0
T_{max1} (h)	1.8 ± 0.6	2.0 ± 0.8	1.9 ± 0.4	2.0 ± 0.9
	1 - 3	1 - 3	1.3 - 2.7	1.3 - 4.0
C_{max1} (ng/mL)	10.2 ± 4.2	10.3 ± 5.1	4.3 ± 2.3	5.3 ± 0.9
	4.2 - 20.2	5.5 - 26.6	1.8 - 7.5	3.8 - 6.9
T_{minip} (h)	4.0 ± 0.2	4.5 ± 1.2	3.8 ± 0.4	3.6 ± 0.6
	4 - 5	2 - 6	3.3 - 4.3	2.7 - 4.3
C_{minip} (ng/mL)	5.8 ± 2.7	6.1 ± 4.1	1.2 ± 1.4	3.0 ± 0.8
	3.1 - 14.4	2.9 - 21.0	0.0 - 3.7	1.7 - 4.0
T_{max2} (h)	5.6 ± 0.7	6.6 ± 1.5	5.9 ± 0.5	5.5 ± 0.8
	5 - 8	5 - 11	5.0 - 6.5	4.3 - 6.5
C_{max2} (ng/mL)	15.3 ± 7.0	10.2 ± 5.9	5.3 ± 1.4	6.2 ± 1.6
	6.2 - 32.8	4.5 - 31.1	3.6 - 7.2	3.9 - 8.3
$AUC_{(0-\infty)}$	102.4 ± 54.6	86.6 ± 64.0[a]	37.8 ± 21.9	45.8 ± 10.0
(ng/mL x h-1)	40.5 - 261.6	43.3 - 301.44	14.3 - 85.3	34.0 - 61.6
$t_{1/2}$ (h)	2.5 ± 0.8	2.4 ± 0.7[a]	3.5 ± 1.9	3.3 ± 0.4
	1.8 - 5.3	1.5 - 4.0	1.3 - 7.7	3.0 - 4.2

[a] N = 15

Dose Proportionality

After oral administration of Ritalin LA 20 mg and 40 mg capsules to adults there is a slight upward trend in the methylphenidate area under the curve (AUC) and peak plasma concentrations (C_{max1} and C_{max2}).

Distribution

Binding to plasma proteins is low (10%-33%), and the apparent distribution volume at steady state with intravenous administration has been reported to be approximately 6 L/kg.

Metabolism

The absolute oral bioavailability of methylphenidate in children has been reported to be about 30% (range 10%-52%), suggesting pronounced presystemic metabolism. Biotransformation of methylphenidate is rapid and extensive leading to the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid (ritalinic acid). Only small amounts of hydroxylated metabolites (e.g., hydroxymethylphenidate and hydroxyritalinic acid) are detectable in plasma. Therapeutic activity is principally due to the parent compound.

Elimination

In studies with Ritalin LA and Ritalin tablets in adults, methylphenidate from Ritalin tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3 - 7.7 hours). In children the average half-life is about 2.5 hours, with a range of about 1.5 - 5.0 hours. The rapid half-life in both children and adults may result in unmeasurable concentrations between the morning and mid-day doses with Ritalin tablets. No accumulation of methylphenidate is expected following multiple once a day oral dosing with Ritalin LA. The half-life of ritalinic acid is about 3-4 hours.

After oral administration of an immediate release formulation of methylphenidate, 78%-97% of the dose is excreted in the urine and 1%-3% in the feces in the form of metabolites within 48-96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60%-86%), the remainder being accounted for by minor metabolites.

Food Effects

Administration times relative to meals and meal composition may need to be individually titrated.

When Ritalin LA was administered with a high fat breakfast to adults, Ritalin LA had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined.

There were no differences in the pharmacokinetics of Ritalin LA when administered with applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered (see DOSAGE AND ADMINISTRATION).

Special Populations

Age: The pharmacokinetics of Ritalin LA was examined in 18 children with ADHD between 7 and 12 years of age. Fifteen of these children were between 10 and 12 years of age. The time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After a 20-mg dose of Ritalin LA, concentrations in children were approximately twice the concentrations observed in 18 to 35 year old adults. This higher exposure is almost completely due to the smaller body size and total volume of distribution in children, as apparent clearance normalized to body weight is independent of age.

Gender: There were no apparent gender differences in the pharmacokinetics of methylphenidate between healthy male and female adults when administered Ritalin LA.

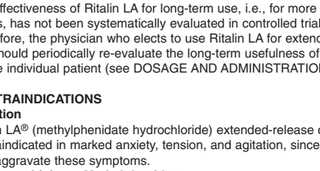
Renal Insufficiency: Ritalin LA has not been studied in renally-impaired patients. Renal insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1% of a radiolabeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity.

Hepatic Insufficiency: Ritalin LA has not been studied in patients with hepatic insufficiency. Hepatic insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body.

CLINICAL STUDIES

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules was evaluated in a randomized, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of attention deficit hyperactivity disorder (ADHD) received a single morning dose of Ritalin LA in the range of 10-40 mg/day, or placebo, for up to 2 weeks. The doses used were the optimal doses established in a previous individual dose titration phase. In that titration phase, 53 of 164 patients (32%) started on a daily dose of 10 mg and 111 of 164 patients (68%) started on a daily dose of 20 mg or higher. The patient's regular schoolteacher completed the Conners ADHD/DSM-IV Scale for Teachers (CADS-T) at baseline and the end of each week. The CADS-T assesses symptoms of hyperactivity and inattention. The change from baseline of the (CADS-T) scores during the last week of treatment was analyzed as the primary efficacy parameter. Patients treated with Ritalin LA showed a statistically significant improvement in symptom scores from baseline over patients who received placebo. (See Figure 2.) This demonstrates that a single morning dose of Ritalin LA exerts a treatment effect in ADHD.

Figure 2. CADS-T total subscale - Mean change from baseline*



*Error bars represent standard error of the mean

INDICATIONS AND USAGE

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Ritalin LA in the treatment of ADHD was established in one controlled trial of children aged 6 to 12 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two 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 six 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 six 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. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome 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 child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

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

Long-Term Use

The effectiveness of Ritalin LA for long-term use, i.e., for more than 2 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Ritalin LA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules is contraindicated in marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

Ritalin LA is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

Ritalin LA is contraindicated in patients with glaucoma.

Tics

Ritalin LA is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (See ADVERSE REACTIONS.)

Monoamine Oxidase Inhibitors

Ritalin LA is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Depression

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules should not be used to treat severe depression.

Fatigue

Ritalin LA should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted. In the double-blind placebo-controlled study of Ritalin LA, the mean weight gain was greater for patients receiving placebo (+1.0 kg) than for patients receiving Ritalin LA (+0.1 kg).

Psychosis

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

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in the absence of seizures, and, very rarely, in the absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, Ritalin LA should be discontinued.

Hypertension and other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking Ritalin LA, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, 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 hyperthyroidism.

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported with methylphenidate.

Use in Children Under Six Years of Age

Ritalin LA should not be used in children under six years of age, since safety and efficacy in this age group have not been established.

Drug Dependence

Ritalin LA should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients

Patient information is provided at the end of this insert. To assure safe and effective use of Ritalin LA® (methylphenidate hydrochloride) extended-release capsules, the patient information should be discussed with patients.

Drug Interactions

Methylphenidate is metabolized primarily by de-esterification (nonmicrosomal hydrolytic esterases) to ritalinic acid and not through oxidative pathways.

The effects of gastrointestinal pH alterations on the absorption of methylphenidate from Ritalin LA have not been studied. Since the modified release characteristics of Ritalin LA are pH dependent, the coadministration of antacids or acid suppressants could alter the release of methylphenidate.

Methylphenidate may decrease the hypotensive effect of guanethidine. Because of possible effects on blood pressure, methylphenidate should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

Carcinogenesis/Mutagenesis/Impairment of Fertility

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or in the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended dose on a mg/kg and mg/m^2 basis, respectively.

Pregnancy

Pregnancy Category C

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Ritalin LA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ritalin LA is administered to a nursing woman.

Pediatric Use

Long-term effects of methylphenidate in children have not been well established. Ritalin LA should not be used in children under six years of age (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

The clinical program for Ritalin LA® (methylphenidate hydrochloride) extended-release capsules consisted of six studies: two controlled clinical studies conducted in children with ADHD aged 6-12 years and four clinical pharmacology studies conducted in healthy adult volunteers. These studies included a total of 256 subjects; 195 children with ADHD and 61 healthy adult volunteers. The subjects received Ritalin LA in doses of 10-40 mg per day. Safety of Ritalin LA was assessed by evaluating frequency and nature of adverse events, routine laboratory tests, vital signs, and body weight.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MEDRA terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment

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Ritalin LA®
(methylphenidate hydrochloride)
extended-release capsules

emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Events in a Double-Blind, Placebo-Controlled Clinical Trial with Ritalin LA

Treatment-Emergent Adverse Events

A placebo-controlled, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of Ritalin LA in children with ADHD aged 6-12 years. All subjects received Ritalin LA for up to 4 weeks, and had their dose optimally adjusted, prior to entering the double-blind phase of the trial. In the two-week double-blind treatment phase of this study, patients received either placebo or Ritalin LA at their individually-titrated dose (range 10 mg-40 mg).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Adverse events with an incidence >5% during the initial four-week single-blind Ritalin LA titration period of this study were headache, insomnia, upper abdominal pain, appetite decreased, and anorexia.

Treatment-emergent adverse events with an incidence >2% among Ritalin LA-treated subjects, during the two-week double-blind phase of the clinical study, were as follows:

Preferred term	Ritalin LA® N=65 N (%)	Placebo N=71 N (%)
Anorexia	2 (3.1)	0 (0.0)
Insomnia	2 (3.1)	0 (0.0)

Adverse Events Associated with Discontinuation of Treatment

In the two-week double-blind treatment phase of a placebo-controlled parallel-group study in children with ADHD, only one Ritalin LA-treated subject (1/65, 1.5%) discontinued due to an adverse event (depression).

In the single-blind titration period of this study, subjects received Ritalin LA for up to 4 weeks. During this period a total of six subjects (6/161, 3.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anger (in 2 patients), hypomania, anxiety, depressed mood, fatigue, migraine and lethargy.

Adverse Events with Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia
Gastrointestinal: abdominal pain, nausea
Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.
Metabolism/Nutrition: anorexia, weight loss during prolonged therapy
Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis
Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: leukopenia and/or anemia
Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma
Psychiatric: transient depressed mood
Skin/Subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules, like other products containing methylphenidate, is a Schedule II controlled substance. (See WARNINGS for boxed warning containing drug abuse and dependence information.)

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center

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

Recommended Treatment

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of methylphenidate from Ritalin LA® (methylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate overdosage has not been established; also, dialysis is considered unlikely to be of benefit due to the large volume of distribution of methylphenidate.

DOSAGE AND ADMINISTRATION

Administration of Dose

Ritalin LA® (methylphenidate hydrochloride) extended-release capsules is for oral administration once daily in the morning. Ritalin LA may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Ritalin LA and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

Dosing Recommendations

Dosage should be individualized according to the needs and responses of the patients.

Initial Treatment

The recommended starting dose of Ritalin LA is 20 mg once daily. Dosage may be adjusted in weekly 10 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending on tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with Ritalin LA 10 mg.

Patients Currently Receiving Methylphenidate

The recommended dose of Ritalin LA for patients currently taking methylphenidate b.i.d. or sustained release (SR) is provided below.

Previous Methylphenidate Dose	Recommended Ritalin LA® Dose
5 mg methylphenidate b.i.d.	10 mg q.d.
10 mg methylphenidate b.i.d. or 20 mg methylphenidate-SR	20 mg q.d.
15 mg methylphenidate b.i.d.	30 mg q.d.
20 mg methylphenidate b.i.d. or 40 mg of methylphenidate-SR	40 mg q.d.
30 mg methylphenidate b.i.d. or 60 mg methylphenidate-SR	60 mg q.d.

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. Ritalin LA dosage may be adjusted at weekly intervals in 10 mg increments.

Daily dosage above 60 mg is not recommended.

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Ritalin LA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Ritalin LA for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED

Ritalin LA capsules 10 mg: white/light brown (imprinted NVR R10)
Bottles of 100 . . . . . .NDC 0078-0424-05
Ritalin LA capsules 20 mg: white (imprinted NVR R20)
Bottles of 100 . . . . . .NDC 0078-0370-05
Ritalin LA capsules 30 mg: yellow (imprinted NVR R30)
Bottles of 100 . . . . . .NDC 0078-0371-05
Ritalin LA capsules 40 mg: light brown (imprinted NVR R40)
Bottles of 100 . . . . . .NDC 0078-0372-05

Store at 25°C (77°F), excursions permitted 15°C-30°C (59°F-86°F). [See USP controlled room temperature]

Dispense in tight container (USP).

Ritalin LA® is a trademark of Novartis AG.
SODAS™ is a trademark of Elan Corporation, plc.
This product is covered by US patents including US 5,837,284 and 6,228,398.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th edition. Washington DC: American Psychiatric Association 1994.

REV: APRIL 2004 T2004-34

T2004-35

INFORMATION FOR PATIENTS TAKING RITALIN LA®, OR FOR THEIR PARENTS OR CAREGIVERS

Once Daily

Ritalin LA®

(methylphenidate hydrochloride)
extended-release capsules

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This information for patients or their parents or caregivers is about Ritalin LA. Please read this before you start taking Ritalin LA. Also, read the information you get each time you renew your prescription, in case anything has changed. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about Ritalin LA, talk to your doctor or pharmacist.

WHAT IS RITALIN LA?

Ritalin LA is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. Ritalin LA contains the drug methylphenidate (Ritalin®), a central nervous system stimulant that has been used to treat ADHD for more than 30 years. Ritalin is available in several forms including Ritalin LA, an extended-release form of methylphenidate hydrochloride available as 10, 20, 30, and 40 mg extended-release capsules. Ritalin LA is taken by mouth, once each day in the morning, before breakfast.

WHAT IS ATTENTION DEFICIT HYPERACTIVITY DISORDER?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

HOW DOES RITALIN LA WORK?

When you take a Ritalin LA capsule, half of the beads provide an immediate dose of methylphenidate and the other half provide a delayed second release of the drug to continue to help lessen the symptoms of ADHD during the day. Methylphenidate, the active ingredient in Ritalin LA, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

BEFORE RITALIN LA TREATMENT

It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that Ritalin is only part of the overall management of ADHD. Parents, teachers, physicians and other professionals are part of a team that must work together.

Before Ritalin treatment, your doctor should be made aware of any current or past physical or mental problems. Tell your doctor if there is a history of drug or alcohol abuse, depression, psychosis, epilepsy or seizure disorders, high blood pressure, glaucoma, facial tics (involuntary movements), or a family history of Tourette's syndrome.

Both your doctor and your pharmacist should also be informed of all medicines that you are taking, even if these drugs are not taken on a regular basis and are available without prescription. Your doctor will decide whether you can take Ritalin with other medicines. Methylphenidate is known to interact with a number of other drugs. These include medicines to treat depression, such as monoamine oxidase inhibitors; to control seizures; and to thin blood. Sometimes these interactions may require a change in dosage, or occasionally stopping one of the drugs involved.

Tell your doctor if you are pregnant or nursing a baby.

WHO SHOULD NOT TAKE RITALIN LA?

You should NOT take Ritalin LA if:

- You have significant anxiety, tension, or agitation since Ritalin LA may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in Ritalin LA.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.
- You are taking a monoamine oxidase inhibitor, a type of drug, or have discontinued a monoamine oxidase inhibitor in the last 14 days.

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

HOW SHOULD I TAKE RITALIN LA?

Take Ritalin LA once each day in the morning.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

Ritalin LA capsules may be taken at the same time as food or without food, although food may delay the absorption of Ritalin LA. The Ritalin LA capsule may be swallowed as whole capsules or the capsule may be opened and sprinkled on a small amount of applesauce. The capsule should not be crushed or chewed or its contents divided.

To sprinkle the contents of the capsule, open the capsule carefully and sprinkle the beads over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

If you also take antiacids or drugs that suppress stomach acids, you should discuss with your physician or pharmacist how to take these drugs with Ritalin LA.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF RITALIN LA?

The most common side effects of Ritalin LA are:

- Nervousness
- Stomach pain
- Sleeplessness
- Decreased appetite

Other side effects seen with methylphenidate, the active ingredient in Ritalin LA, include nausea, vomiting, dizziness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

Dependence

Abuse of methylphenidate 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.

Blurred Vision

Tell your doctor if you have blurred vision when taking Ritalin LA. This could be a sign of a serious problem.

Slower Growth

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your Ritalin LA treatment.

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

WHAT MUST I DISCUSS WITH MY DOCTOR BEFORE TAKING RITALIN LA?

Talk to your doctor ***before*** taking RITALIN LA if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have an abnormal heart rate or rhythm.

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking Ritalin LA.

CAN I TAKE RITALIN LA WITH OTHER MEDICINES?

Tell your doctor about ***all*** medicines that you are taking or intend to take. Your doctor should decide whether you can take Ritalin LA with other medicines. These include:

- Other medicines that a doctor has prescribed.
- All medicines that you buy yourself without a prescription.
- Any herbal remedies that you may be taking.

Monoamine Oxidase (MAO) Inhibitors

You should not take Ritalin LA with (MAO) inhibitors or within 14 days of stopping a MAO inhibitor.

Starting a New Medicine

While on Ritalin LA, do not start taking a new medicine or herbal remedy before checking with your doctor.

Other Medicines You May Be Taking

Ritalin LA may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with Ritalin LA.

Other Important Safety Information

Pregnancy and Nursing

Before taking Ritalin LA, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Overdose

Call your doctor ***immediately*** if you take more than the amount of Ritalin LA prescribed by your doctor.

WHAT ELSE SHOULD I KNOW ABOUT RITALIN LA?

Ritalin LA has not been studied in children under 6 years of age.

Ritalin LA may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share Ritalin LA with anyone else and take only the number of Ritalin LA capsules prescribed by your doctor.

Ritalin LA should be stored in a safe place at room temperature (between 59°F-86°F). Do not store this medicine in hot, damp, or humid places. Keep the container of Ritalin LA in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication. Keep track of the number of capsules so that you will know if any are missing. Someone who has easy access to Ritalin may be able to give the capsules to others or misuse the medication.

Keep out of the reach of children.

This leaflet summarizes the most important information about Ritalin LA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Ritalin LA that is written for health professionals.

You can also call 1-888 NOWNOVA (1-888-669-6682).

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NOVARTIS

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
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Pharmaceutical Division
Gainesville, GA 30504

NOVARTIS

T2005-48
5000450

Ritalin® hydrochloride
methylphenidate hydrochloride tablets USP

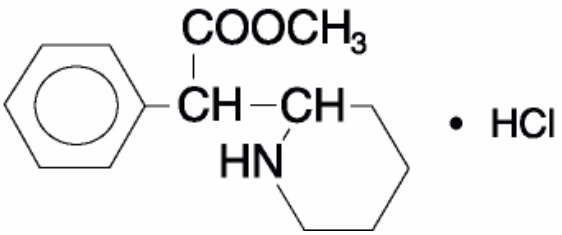
Ritalin-SR®
methylphenidate hydrochloride USP sustained-release tablets

Rx only

Prescribing Information

DESCRIPTION

Ritalin hydrochloride, methylphenidate hydrochloride USP, is a mild central nervous system (CNS) stimulant, available as tablets of 5, 10, and 20 mg for oral administration; Ritalin-SR is available as sustained-release tablets of 20 mg for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive Ingredients. Ritalin tablets: D&C Yellow No. 10 (5-mg and 20-mg tablets), FD&C Green No. 3 (10-mg tablets), lactose, magnesium stearate, polyethylene glycol, starch (5-mg and 10-mg tablets), sucrose, talc, and tragacanth (20-mg tablets).

Ritalin-SR tablets: Cellulose compounds, cetostearyl alcohol, lactose, magnesium stearate, mineral oil, povidone, titanium dioxide, and zein.

CLINICAL PHARMACOLOGY

Ritalin is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but Ritalin presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

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

Ritalin in the SR tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the SR tablet compared to the Ritalin tablet, measured by the urinary excretion of Ritalin major metabolite (α-phenyl-2-piperidine acetic acid) was 105% (49%-168%) in children and 101% (85%-152%) in adults. The time to peak rate in children was 4.7 hours (1.3-8.2 hours) for the SR tablets and 1.9 hours (0.3-4.4 hours) for the tablets. An average of 67% of SR tablet dose was excreted in children as compared to 86% in adults.

In a clinical study involving adult subjects who received SR tablets, plasma concentrations of Ritalin's major metabolite appeared to be greater in females than in males. No gender differences were observed for Ritalin plasma concentration in the same subjects.

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is 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 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.

Special Diagnostic Considerations

Specific etiology of this syndrome 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.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in

patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Ritalin is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking Ritalin especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, 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, cardiac arrhythmia, or hyperthyroidism.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin 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 Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

Carcinogenesis/Mutagenesis/Impairment of Fertility

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or in the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methlyphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended dose on a mg/kg and mg/m^2 basis, respectively.

PREGNANCY

Pregnancy Category C

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Ritalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ritalin is administered to a nursing woman.

Pediatric Use

Long-term effects of methylphenidate in children have not been well established. Ritalin should not be used in children under six years of age (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura);

anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; aggressive behavior; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

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

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate before performing gastric lavage. Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Ritalin overdosage has not been established.

HOW SUPPLIED

Tablets 5 mg - round, yellow (imprinted CIBA 7)
Bottles of 100 ..... NDC 0078-0439-05

Tablets 10 mg - round, pale green, scored (imprinted CIBA 3)
Bottles of 100 ..... NDC 0078-0440-05

Tablets 20 mg - round, pale yellow, scored (imprinted CIBA 34)
Bottles of 100 ..... NDC 0078-0441-05

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.
Dispense in tight, light-resistant container (USP).

SR Tablets 20 mg - round, white, coated (imprinted CIBA 16)
Bottles of 100 ..... NDC 0078-0442-05

Note: SR Tablets are color-additive free.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Dispense in tight, light-resistant container (USP).

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NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Focalin™

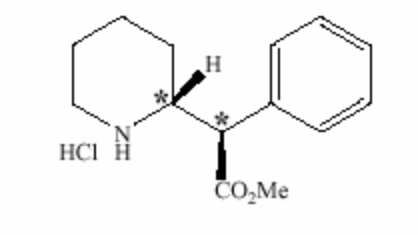
dexmethylphenidate hydrochloride tablets

Rx Only

Prescribing Information

DESCRIPTION

Focalin™ (dexmethylphenidate hydrochloride) is the d-threo-enantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of the d-threo and l-threo-enantiomers. Focalin is a central nervous system (CNS) stimulant, available in three tablet strengths. Each tablet contains dexmethylphenidate hydrochloride 2.5, 5, or 10 mg for oral administration. Dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its molecular weight is 269.77 and its structural formula is



Note: * = asymmetric carbon centers

Dexmethylphenidate hydrochloride is a white to off white powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Focalin also contains the following inert ingredients: pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C Blue No.1 #5516 aluminum lake (2.5 mg tablets), D&C Yellow Lake #10 (5 mg tablets); the 10 mg tablet contains no dye.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Dexmethylphenidate hydrochloride is a central nervous system stimulant. Focalin, the more pharmacologically active enantiomer of the d- and l-enantiomers, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

Pharmacokinetics

Absorption

Dexmethylphenidate hydrochloride is readily absorbed following oral administration of Focalin. In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum in the fasted state at about 1 to 1½ hours post-dose. No differences in the pharmacokinetics of Focalin were noted following single and repeated twice daily dosing, thus indicating no significant drug accumulation in children with ADHD.

When given to children as capsules in single doses of 2.5 mg, 5 mg, and 10 mg, C_{max} and $AUC_{0\text{-}inf}$ of dexmethylphenidate were proportional to dose. In the same study, plasma dexmethylphenidate levels were comparable to those achieved following single dl-threo-methylphenidate HCl doses given as capsules in twice the total mg amount (equimolar with respect to Focalin).

Food Effects

In a single dose study conducted in adults, coadministration of 2 x 10 mg Focalin with a high fat breakfast resulted in a dexmethylphenidate t_{max} of 2.9 hours post-dose as compared to 1.5 hours post-dose when given in a fasting state. C_{max} and $AUC_{0\text{-}inf}$ were comparable in both the fasted and non-fasted states.

Distribution

Plasma dexmethylphenidate concentrations in children decline exponentially following oral administration of Focalin.

Metabolism and Excretion

In humans, dexmethylphenidate is metabolized primarily to d-α-phenyl-piperidine acetic acid (also known as d-ritalinic acid) by de-esterification. This metabolite has little or no pharmacological activity. There is little or no in vivo interconversion to the l-threo-enantiomer, based on a finding of minute levels of l-threo-methylphenidate being detectable in a few samples in only 2 of 58 children and adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose.

In vitro studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes.

The mean plasma elimination half-life of dexmethylphenidate is approximately 2.2 hours.

Special Populations

Gender

Pharmacokinetic parameters were also similar for boys and girls (mean age 10 years).

In a single dose study conducted in adults, the mean dexmethylphenidate AUC_{0-inf} values (adjusted for body weight) following single 2 x 10 mg doses of Focalin were 25%-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both t_{max} and $t_{1/2}$ were comparable for males and females.

Race

There is insufficient experience with the use of Focalin to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of dexmethylphenidate after Focalin administration have not been studied in children less than 6 years of age. When single doses of Focalin were given to children between the ages of 6 to 12 years and healthy adult volunteers, C_{max} of dexmethylphenidate was similar, however, children showed somewhat lower AUCs compared to the adults.

Renal Insufficiency

There is no experience with the use of Focalin in patients with renal insufficiency. After oral administration of radiolabeled racemic methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since very little unchanged drug is excreted in the urine, renal insufficiency is expected to have little effect on the pharmacokinetics of Focalin.

Hepatic Insufficiency

There is no experience with the use of Focalin in patients with hepatic insufficiency. (For Drug Interactions, see PRECAUTIONS.)

Clinical Studies

Focalin was evaluated in two double-blind, parallel-group, placebo-controlled trials in untreated or previously treated patients aged 6 to 17 years old with a DSM-IV diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Both studies included all three subtypes of ADHD, i.e., Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type. While both children and adolescents were included, the sample was predominantly children, thus, the findings are most pertinent to this age group. In both studies, the primary comparison of interest was Focalin versus placebo.

Focalin (5, 10, or 20 mg/day total dose), dl-threo-methylphenidate HCl (10, 20, or 40 mg/day total dose), and placebo were compared in a multicenter, 4-week, parallel group study in n=132 patients. Patients took the study medication twice daily, 3.5 to 5.5 hours between doses. Treatment was initiated with the lowest dose, and doses could be doubled at weekly intervals, depending on clinical response and tolerability, up to the maximum dose. The change from baseline to week 4 of the averaged score (an average of two ratings during the week) of the teacher's version of the SNAP-ADHD Rating Scale, a scale for assessing ADHD symptoms, was the primary

outcome. Patients treated with Focalin showed a statistically significant improvement in symptom scores from baseline over patients who received placebo.

Figure 1

Mean Change from Baseline in Teacher SNAP-ADHD Scores in a 4-week Double-Blind Placebo-Controlled Study of Focalin™*

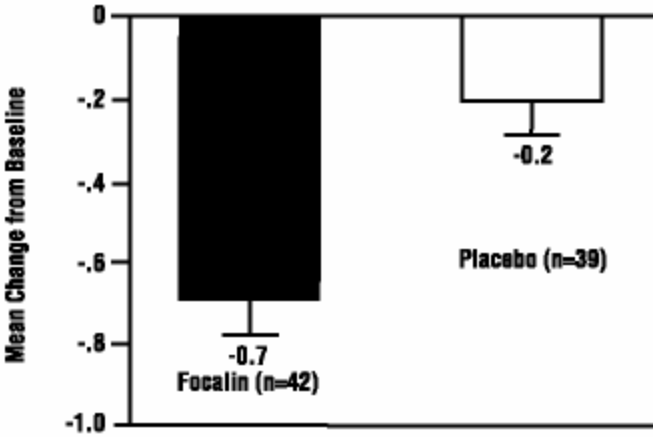
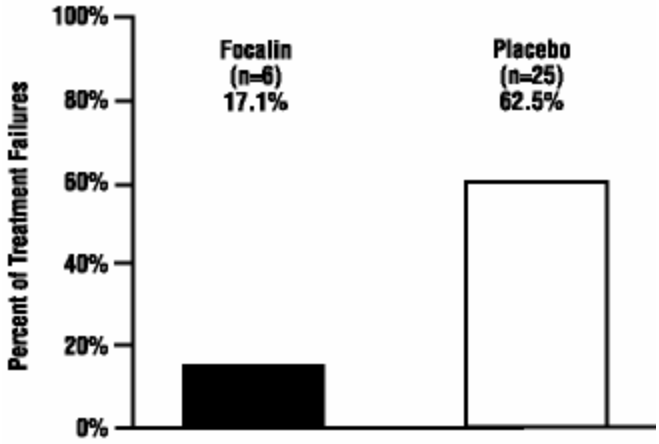


*Figure 1: Error bars represent the standard error of the mean.

The other study, involving n=75 patients, was a multicenter, placebo-controlled, double-blind, 2-week treatment withdrawal study in children who were responders during a 6-week, open label initial treatment period. Children took study medication twice a day separated by a 3.5 to 5.5 hour interval. The primary outcome was proportion of treatment failures at the end of the 2-week withdrawal phase, where treatment failure was defined as a rating of 6 (much worse) or 7 (very much worse) on the Investigator Clinical Global Impression - Improvement (CGI-I). Patients continued on Focalin showed a statistically significant lower rate of failure over patients who received placebo.

Figure 2

Percent of Treatment Failures following a 2-week Double-Blind Placebo-Controlled Withdrawal of Focalin™



INDICATION AND USAGE

Focalin is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Focalin in the treatment of ADHD was established in two controlled trials of patients aged 6 to 17 years of age who met DSM-IV criteria for ADHD (see Clinical Studies).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning; and be present in two 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 six 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 six 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. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome 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 child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

Focalin is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are 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 and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-term Use

The effectiveness of Focalin for long-term use, i.e., for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Focalin for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

Focalin is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

Focalin is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

Focalin is contraindicated in patients with glaucoma.

Tics

Focalin is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

Focalin is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Depression

Focalin should not be used to treat severe depression.

Fatigue

Focalin should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Sufficient data on safety of long-term use of Focalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

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

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Hypertension and Other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Focalin, especially those with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both Focalin and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mmHg, compared to placebo. Therefore, 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 hyperthyroidism.

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases following use of methylphenidate. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under 6 Years of Age

Focalin should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE: Focalin should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients

Patient information is printed at the end of this insert. To assure safe and effective use of Focalin, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Because of possible effects on blood pressure, Focalin should be used cautiously with pressor agents.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relativity rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week study of racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60-74 mg/kg/day of racemic methylphenidate.

Dexmethylphenidate was not mutagenic in the in vitro Ames reverse mutation assay, the in vitro mouse lymphoma cell forward mutation assay, or the in vivo mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay, and was negative in vivo in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day.

Pregnancy

Pregnancy Category C

In studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels (AUCs) of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with the maximum recommended human dose of 20 mg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. Focalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Focalin is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Focalin in children under 6 years old have not been established. Long-term effects of Focalin in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The pre-marketing development program for Focalin included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received Focalin 5, 10, or 20 mg/day. The 684 ADHD patients (ages 6 to 17 years) were evaluated in two controlled clinical studies, two clinical pharmacology studies, and two uncontrolled long-term safety studies. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, and results of physical examinations, vital sign and body weight measurements, and laboratory analyses.

Adverse events during exposure were primarily obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion ofindividuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with Focalin

Adverse Events Associated with Discontinuation of Treatment

No Focalin-treated patients discontinued due to adverse events in two placebo-controlled trials. Overall, 50 of 684 children treated with Focalin (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

Adverse Events Occurring at an Incidence of 5% or More Among Focalin-Treated Patients

Table 1 enumerates treatment-emergent adverse events for two, placebo-controlled, parallel group trials in children with ADHD at Focalin doses of 5, 10, and 20 mg/day. The table includes only those events that occurred in 5% or more of patients treated with Focalin where the incidence in patients treated with Focalin was at least twice the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment in Clinical Trials of Focalin™

Body System	Preferred Term	Focalin (n=79)	Placebo (n=82)
Body as a Whole			
	Abdominal Pain	15%	6%
	Fever	5%	1%
Digestive System			
	Anorexia	6%	1%
	Nausea	9%	1%

1 Events, regardless of causality, for which the incidence for patients treated with Focalin was at least 5% and twice the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased

Gastrointestinal: nausea

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood

Skin/subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Focalin, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdosage has not been established.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

DOSAGE AND ADMINISTRATION

Focalin is administered twice daily, at least 4 hours apart. Focalin may be administered with or without food.

Dosage should be individualized according to the needs and responses of the patient.

Patients New to Methylphenidate

The recommended starting dose of Focalin for patients who are not currently taking racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day (2.5 mg twice daily).

Dosage may be adjusted in 2.5 to 5 mg increments to a maximum of 20 mg/day (10 mg twice daily). In general, dosage adjustments may proceed at approximately weekly intervals.

Patients Currently Using Methylphenidate

For patients currently using methylphenidate, the recommended starting dose of Focalin is half the dose of racemic methylphenidate. The maximum recommended dose is 20 mg/day (10 mg twice daily).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Focalin. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Focalin for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

HOW SUPPLIED

Tablets, D-shaped, embossed "D" on upper convex face and dosage strength on lower convex face

2.5 mg Tablets - blue
Bottles of 100..... NDC 0078-0380-05

5 mg Tablets - yellow
Bottles of 100..... NDC 0078-0381-05

10 mg Tablets - white
Bottles of 100..... NDC 0078-0382-05

Store at 25°C (77°F); excursions permitted 15°C-30°C (59°F-86°F).

[see USP Controlled Room Temperature]

Protect from light and moisture.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

REV: NOVEMBER 2001

INFORMATION FOR PATIENTS TAKING FOCALIN™, OR FOR THEIR PARENTS OR CAREGIVERS

Focalin™

Dexmethylphenidate hydrochloride tablets 

This information for patients or their parents or caregivers is about Focalin, a medication intended for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Please read this before you start taking Focalin. It is not intended to replace your doctor's instructions or advice. If you have any questions about this material or about Focalin, be sure to talk to your doctor or pharmacist.

What is Focalin?

Focalin is a central nervous system stimulant for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Dexmethylphenidate hydrochloride, the active ingredient of Focalin, is also found in methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. Focalin is available in a D-shaped tablet form, 2.5 mg, 5 mg, and 10 mg, and is intended to be used in doses of 5 to 20 mg per day, given as divided doses, as directed by your doctor.

What is Attention Deficit Hyperactivity Disorder (ADHD)?

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder characterized by symptoms of inattentiveness and/or hyperactivity-impulsivity inappropriate to the patient's age which interfere with functioning in two or more settings (e.g., school and home). Symptoms of inattention may include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity-impulsiveness may include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have both types of symptoms. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How Does Focalin work?

Focalin (dexmethylphenidate hydrochloride) is rapidly absorbed into the bloodstream and acts for a period of several hours. Focalin helps to increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Before Focalin Treatment

It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that Focalin is only part of the overall management of ADHD. Parents, teachers, physicians and other professionals are part of a team that must work together.

Before Focalin treatment, your doctor should be made aware of any current or past physical or mental problems. Tell your doctor if there is a history of drug or alcohol abuse, depression, psychosis, epilepsy or seizure disorders, high blood pressure, glaucoma, facial tics (involuntary movements), or a family history of Tourette's syndrome.

Both your doctor and your pharmacist should also be informed of all medicines that you are taking, even if these drugs are not taken on a regular basis and are available without prescription. Your doctor will decide whether you can take Focalin with other medicines. Methylphenidate is known to interact with a number of other drugs. These include medicines to treat depression, such as monoamine oxidase inhibitors; to control seizures; and to thin blood. Sometimes these interactions may require a change in dosage, or occasionally stopping one of the drugs involved.

Tell your doctor if you are pregnant or nursing a baby.

Who Should Not Take Focalin?

You should NOT take Focalin if:

- You have significant anxiety, tension, or agitation since Focalin may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in Focalin.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.
- You are taking a monoamine oxidase inhibitor, a type of drug, or have discontinued a monoamine oxidase inhibitor in the last 14 days.

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

How Should I Take Focalin?

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the Possible Side Effects of Focalin?

In the clinical studies with patients using Focalin, the most common side effects were stomach pain, fever, decreased appetite, and nausea. Other side effects seen with Focalin include vomiting, dizziness, sleeplessness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What Must I Discuss with my Doctor before Taking Focalin?

Talk to your doctor ***before*** taking Focalin if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have an abnormal heart rate or rhythm.

Tell you doctor ***immediately*** if you develop any of the above conditions or symptoms while taking Focalin.

Can I Take Focalin with Other Medicines?

Tell you doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take Focalin with other medicines. These include:

- Other medicines that a doctor has prescribed.
- Medicines that you buy yourself without a prescription.
- Any herbal remedies that you may be taking.

You should not take Focalin with monoamine oxidase (MAO) inhibitors.

While on Focalin, do not start taking a new medicine or herbal remedy before checking with your doctor.

Focalin may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with Focalin.

Other Important Safety Information

Abuse of Focalin 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.

Before taking Focalin, tell your doctor if you are pregnant or plan on becoming pregnant. If you take Focalin, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking Focalin.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your Focalin treatment.

Call your doctor ***immediately*** if you take more than the amount of Focalin prescribed by your doctor.

What Else Should I Know about Focalin?

Focalin has not been studied in children under 6 years of age.

Focalin may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share Focalin with anyone else and take only the number of Focalin tablets prescribed by your doctor.

Focalin may be taken at the same time as food or with no food. Focalin should be stored in a safe place at room temperature (between 59°F - 86°F). Do not store this medicine in hot, damp, or humid places.

Keep the container of Focalin in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication. Keep track of the number of tablets so that you will know if any are missing. Sadly, someone who has easy access to Focalin may be able to give the tablets to others or misuse the medication.

Keep Out of the Reach of Children

REV:NOVEMBER 2001 Printed in U.S.A.

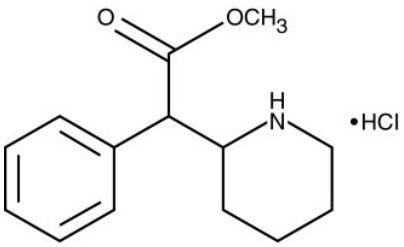
Manufactured for:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

By:
Mikart, Inc.
Atlanta, GA 30318

Once Daily
Metadate® CD
(methylphenidate HCl, USP)
Extended-Release Capsules
Rx only
R312F
Rev. 9/03

DESCRIPTION: METADATE CD is a central nervous system (CNS) stimulant. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component and 70% of the dose is provided by the ER component. METADATE CD is available in three capsule strengths containing 10 mg (3 mg IR; 7 mg ER), 20 mg (6 mg IR; 14 mg ER), or 30 mg (9 mg IR; 21 mg ER) of methylphenidate hydrochloride for oral administration.

Chemically, methylphenidate HCl is *d,l* (racemic)-*threo*-methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its structural formula is:



Methylphenidate HCl USP is a white, odorless, crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77

METADATE CD also contains the following inert ingredients: Sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, FD&C Blue No. 2, FDA/E172 Yellow Iron Oxide (10 mg capsules), FDA/E172 Red Iron Oxide (30 mg capsules).

CLINICAL PHARMACOLOGY: Pharmacodynamics: Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d-* and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

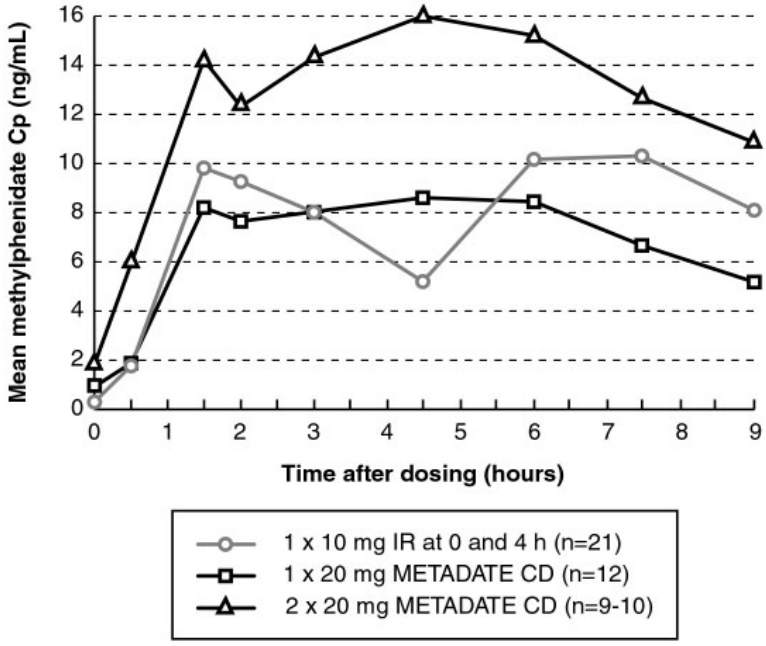
Pharmacokinetics: The pharmacokinetics of the METADATE CD methylphenidate hydrochloride formulation have been studied in healthy adult volunteers and in children with Attention Deficit Hyperactivity Disorder (ADHD).

Absorption and Distribution: Methylphenidate is readily absorbed. METADATE CD has a plasma/time concentration profile showing two phases of drug release with a sharp, initial slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline. (See Figure 1 below.)

Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD: METADATE CD was administered as repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (±SD) early C_{max} was 8.6 (±2.2) ng/mL, the later C_{max} was 10.9 (±3.9)* ng/mL and AUC_{0-9h} was 63.0 (±16.8) ng•h/mL. The corresponding values after a 40 mg dose were 16.8 (±5.1) ng/mL, 15.1 (±5.8)* ng/mL and 120 (±39.6) ng•h/mL, respectively. The early peak concentrations (median) were reached about 1.5 hours after dose intake, and the second peak concentrations (median) were reached about 4.5 hours after dose intake. The means for C_{max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours.

*25-30% of the subjects had only one observed peak (C_{max}) concentration of methylphenidate.

FIGURE 1
Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD



Dose Proportionality: Following single oral doses of 10-60 mg methylphenidate free base as a solution given to ten healthy male volunteers, C_{max} and AUC increased proportionally with increasing doses. After the 60 mg dose, t_{max} was reached 1.5 hours post-dose, with a mean C_{max} of 31.8 ng/mL (range 24.7-40.9 ng/mL).

Following one week of repeated once-daily doses of 20 mg or 40 mg METADATE CD to children aged 7-12 years with ADHD, C_{max} and AUC were proportional to the administered dose.

Food Effects: In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of a dose of 40 mg, the presence of food delayed the early peak by approximately 1 hour (range -2 to 5 hours delay). The plasma levels rose rapidly following the food-induced delay in absorption. Overall, a high-fat meal increased the C_{max} of METADATE CD by about 30% and AUC by about 17%, on average (see DOSAGE and ADMINISTRATION).

After a single dose, the bioavailability (C_{max} and AUC) of methylphenidate in 26 healthy adults was unaffected by sprinkling the capsule contents on applesauce as compared to the intact capsule. This finding demonstrates that a 20 mg METADATE CD Capsule, when opened and sprinkled on one tablespoon of applesauce, is bioequivalent to the intact capsule.

Metabolism and Excretion: In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (ritalinic acid). The metabolite has little or no pharmacologic activity.

In vitro studies showed that methylphenidate was not metabolized by cytochrome P450 isoenzymes, and did not inhibit cytochrome P450 isoenzymes at clinically observed plasma drug concentrations.

The mean terminal half-life ($t_{½}$) of methylphenidate following administration of METADATE CD ($t_{½}$=6.8h) is longer than the mean terminal ($t_{½}$) following administration of methylphenidate hydrochloride immediate-release tablets ($t_{½}$=2.9h) and methylphenidate hydrochloride sustained-release tablets ($t_{½}$=3.4h) in healthy adult volunteers. This suggests that the elimination process observed for METADATE CD is controlled by the release rate of methylphenidate from the extended-release formulation, and that the drug absorption is the rate-limiting process.

Special Populations: Gender: The pharmacokinetics of methylphenidate after a single dose of METADATE CD were similar between adult men and women.

Race: The influence of race on the pharmacokinetics of methylphenidate after METADATE CD administration has not been studied.

Age: The pharmacokinetics of methylphenidate after METADATE CD administration have not been studied in children less than 6 years of age.

Renal Insufficiency: There is no experience with the use of METADATE CD in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans,

methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of METADATE CD.

Hepatic Insufficiency: There is no experience with the use of METADATE CD in patients with hepatic insufficiency.

CLINICAL STUDIES: METADATE CD was evaluated in a double-blind, parallel-group, placebo-controlled trial in which 321 untreated or previously treated pediatric patients with a DSM-IV diagnosis of attention deficit hyperactivity disorder (ADHD), 6 to 15 years of age, received a single morning dose for up to 3 weeks. Patients were required to have the combined or predominantly hyperactive-impulsive subtype of ADHD; patients with the predominantly inattentive subtype were excluded. Patients randomized to the METADATE CD group received 20 mg daily for the first week. Their dosage could be increased weekly to a maximum of 60 mg by the third week, depending on individual response to treatment.

The patient's regular school teacher completed the teachers' version of the Conners' Global Index Scale (TCGIS), a scale for assessing ADHD symptoms, in the morning and again in the afternoon on three alternate days of each treatment week. The change from baseline of the overall average (i.e., an average of morning and afternoon scores over 3 days) of the total TCGIS scores during the last week of treatment was analyzed as the primary efficacy parameter. Patients treated with METADATE CD showed a statistically significant improvement in symptom scores from baseline over patients who received placebo. (See Figure 2.) Separate analyses of TCGIS scores in the morning and afternoon revealed superiority in improvement with METADATE CD over placebo during both time periods. (See Figure 3.) This demonstrates that a single morning dose of METADATE CD exerts a treatment effect in both the morning and the afternoon.

FIGURE 2

Least Squares Mean Change
from Baseline in TCGIS Scores*

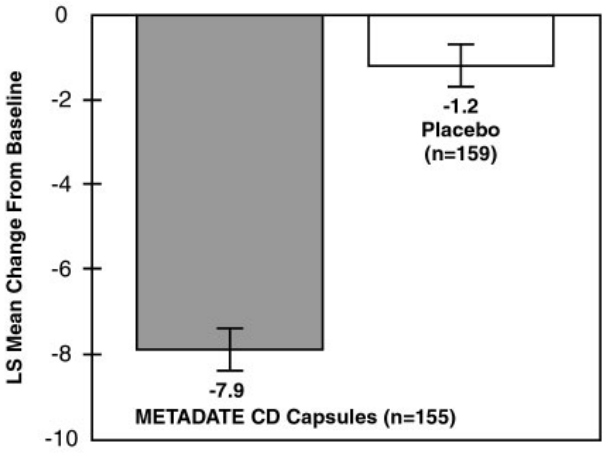
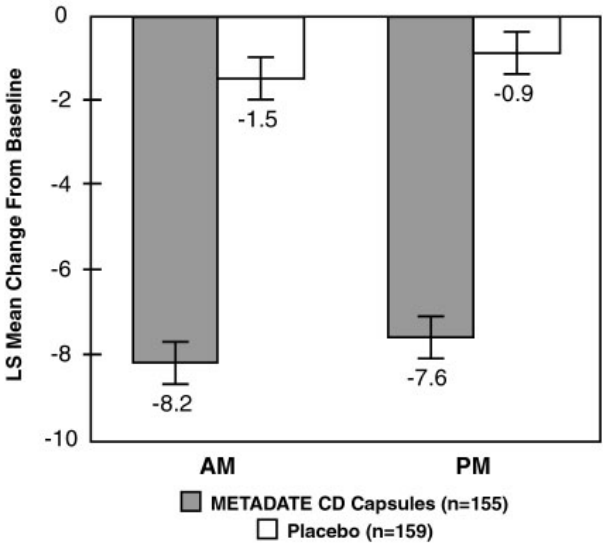


FIGURE 3

Least Squares Mean Change from Baseline
in TCGIS Scores, Morning/Afternoon Groups*



* **FIGURES 2 & 3:** Last observation carried forward analysis at week 3.
Error bars represent the standard error of the mean.

INDICATION AND USAGE: Attention Deficit Hyperactivity Disorder (ADHD):

METADATE® CD (methylphenidate HCl, USP) Extended-Release Capsules are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of METADATE CD in the treatment of ADHD was established in one controlled trial of children aged 6 to 15 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present

before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two 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 six 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 six 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. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome 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 child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program: METADATE CD is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of METADATE CD for long-term use, i.e., for more than 3 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use METADATE CD for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE and ADMINISTRATION).

CONTRAINDICATIONS: Agitation: METADATE CD is contraindicated in patients with marked anxiety, tension and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: METADATE CD is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma: METADATE CD is contraindicated in patients with glaucoma.

Tics: METADATE CD is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors: METADATE CD is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS: Depression: METADATE CD should not be used to treat severe depression.

Fatigue: METADATE CD should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth: Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis: Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures: There is some clinical evidence that methylphenidate 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 absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Hypertension and other Cardiovascular Conditions: Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking METADATE CD, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, 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 hyperthyroidism.

Visual Disturbance: Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age: METADATE® CD (methylphenidate HCl, USP) Extended-Release Capsules should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE: METADATE CD should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS: Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be instructed to take one dose in the morning before breakfast. The patients should be instructed that the capsule may be swallowed whole, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use. The capsules and the capsule contents must not be crushed or chewed.

Patient information is printed along with this insert. To assure safe and effective use of METADATE CD, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions: Because of possible effects on blood pressure, METADATE CD should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of teratogenicity at an oral dose of 58 mg/kg/day. However, this dose, which caused some maternal toxicity, resulted in decreased postnatal pup weights and survival when given to the dams from day one of gestation through the lactation period. This dose is approximately 30 fold and 6 fold the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

There are no adequate and well-controlled studies in pregnant women. METADATE CD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if METADATE CD is administered to a nursing woman.

Pediatric Use: The safety and efficacy of METADATE CD in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS: The premarketing development program for METADATE CD included exposures in a total of 228 participants in clinical trials (188 pediatric patients with ADHD, 40 healthy adult subjects). These participants received METADATE CD 20, 40, and/or 60 mg/day. The 188 patients (ages 6 to 15) were evaluated in one controlled clinical study, one controlled, crossover clinical study, and one uncontrolled clinical study. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events

without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with METADATE CD: Adverse Events Associated with Discontinuation of Treatment: In the 3-week placebo-controlled, parallel-group trial, two METADATE CD-treated patients (1%) and no placebo-treated patients discontinued due to an adverse event (rash and pruritus; and headache, abdominal pain, and dizziness, respectively).

Adverse Events Occurring at an Incidence of 5% or more Among METADATE CD-Treated Patients: Table 1 enumerates, for a pool of the three studies in pediatric patients with ADHD, at METADATE CD doses of 20, 40, or 60 mg/day, the incidence of treatment-emergent adverse events. One study was a 3-week placebo-controlled, parallel-group trial, one study was a controlled, crossover trial, and the third study was an open titration trial. The table includes only those events that occurred in 5% or more of patients treated with METADATE CD where the incidence in patients treated with METADATE CD was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1
Incidence of Treatment-Emergent Events[1]
in a Pool of 3-4 Week Clinical Trials of METADATE CD

Body System	Preferred Term	METADATE CD (n=188)	Placebo (n=190)
General	Headache	12%	8%
	Abdominal pain (stomach ache)	7%	4%
Digestive System	Anorexia (loss of appetite)	9%	2%
Nervous System	Insomnia	5%	2%

[1]: Events, regardless of causality, for which the incidence for patients treated with

METADATE CD was at least 5% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events with Other Methylphenidate HCl Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's Syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been reported, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: METADATE CD, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE: Signs and Symptoms: Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a

cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for METADATE CD overdosage has not been established.

The prolonged release of methylphenidate from METADATE CD should be considered when treating patients with overdose.

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

DOSAGE AND ADMINISTRATION: METADATE CD is administered once daily in the morning, before breakfast.

METADATE CD may be swallowed whole with the aid of liquids, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use. Drinking some fluids, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed. (See PRECAUTIONS: Information for Patients.)

Dosage should be individualized according to the needs and responses of the patient.

Initial Treatment: The recommended starting dose of METADATE CD is 20 mg once daily. Dosage may be adjusted in weekly 10-20 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending upon tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended.

Maintenance/Extended Treatment: There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with METADATE CD. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use METADATE CD for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation: If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED: METADATE CD (methylphenidate HCl, USP) Extended-Release Capsules are available in three strengths:

10 mg, green/white capsules, imprinted with "CELLTECH 574" in white letters on the green cap, and "10 mg" in black letters on the white body of the capsule.

NDC 53014-574-07	Bottle of 100 Capsules
NDC 53014-574-72	Carton of 100 Capsules, Unit Dose

20 mg, blue/white capsules, imprinted with "CELLTECH 575" in white letters on the blue cap, and "20 mg" in black letters on the white body of the capsule.

NDC 53014-575-07	Bottle of 100 Capsules
NDC 53014-575-72	Carton of 100 Capsules, Unit Dose
NDC 53014-575-30	Dose Pack of 30 Capsules*

30 mg, reddish-brown/white capsules, imprinted with "CELLTECH 576" in white letters on the reddish-brown cap, and "30 mg" in black letters on the white body of the capsule.

NDC 53014-576-07	Bottle of 100 Capsules
NDC 53014-576-72	Carton of 100 Capsules, Unit Dose

**** PHARMACIST:*** Dispense only in current dose pack.

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

Keep out of the reach of children.

Reference: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington D.C.: American Psychiatric Association 1994.

For more information call 1-888-METADATE (1-888-638-2328) or visit www.metadate-cd.com

CELLTECH

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Rev. 9/03
R312F

INFORMATION FOR PATIENTS TAKING METADATE® CD OR THEIR PARENTS OR CAREGIVERS

Once Daily
Metadate® CD
(methylphenidate HCl, USP)
Extended-Release Capsules

This information is for patients or their parents or caregivers taking METADATE CD Capsules for the treatment of Attention Deficit Hyperactivity Disorder.

Please read this before you start taking METADATE CD. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about METADATE CD, talk to your doctor or pharmacist.

What is METADATE® CD?

METADATE CD is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. METADATE CD contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. METADATE CD is taken by mouth, once each day in the morning, before breakfast.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does METADATE® CD work?

The METADATE CD capsule dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in METADATE CD, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take METADATE® CD?

You should NOT take METADATE CD if:

• You have significant anxiety, tension, or agitation since METADATE CD may make these conditions worse.
• You are allergic to methylphenidate or any of the other ingredients in METADATE CD.
• You have glaucoma, an eye disease.
• You have tics or Tourette's Syndrome, or a family history of Tourette's Syndrome.

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

How should I take METADATE® CD?

Do not chew or crush the capsules or the beads inside the capsule. Swallow the METADATE CD Capsules whole with the help of water or other liquids, such as milk or juice. Alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and taken immediately (do not store for future use) without chewing. Take a drink of water after the sprinkles with applesauce have been swallowed.

Take METADATE CD once each day in the morning, before breakfast.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of METADATE® CD?

In the clinical studies with patients using METADATE CD, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in METADATE CD, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking METADATE® CD (methylphenidate HCl, USP) Extended-Release Capsules?

Talk to your doctor **before** taking METADATE CD if you:

• Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
• Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
• Have someone in your family with motion tics, verbal tics, or Tourette's Syndrome.
• Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
• Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).

• Have high blood pressure.

Tell your doctor **immediately** if you develop any of the above conditions or symptoms while taking METADATE CD.

Can I take METADATE® CD with other medicines?

Tell your doctor about **all** medicines that you are taking or intend to take. Your doctor should decide whether you can take METADATE CD with other medicines. These include:

• Other medicines that a doctor has prescribed.
• All medicines that you buy yourself without a prescription.
• Any herbal remedies that you may be taking.

You should not take METADATE CD with monoamine oxidase (MAO) inhibitors.

While on METADATE CD, do not start taking a new medicine or herbal remedy before checking with your doctor.

METADATE CD may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with METADATE CD.

Other Important Safety Information:

Abuse of methylphenidate 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.

Before taking METADATE CD, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking METADATE CD.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your METADATE CD treatment.

Call your doctor **immediately** if you take more than the amount of METADATE CD prescribed by your doctor.

What else should I know about METADATE® CD?

METADATE CD has not been studied in children under 6 years of age.

METADATE CD may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share METADATE CD with anyone else and take only the number of METADATE CD Capsules prescribed by your doctor.

METADATE CD should be stored in a safe place at room temperature (between 59°-86°F).

Keep out of the reach of children.

For more information call
1-888-METADATE (1-888-638-2328)
or visit www.metadate-cd.com

CELLTECH

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

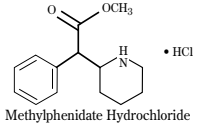
Rev. 9/03
R312F

Methylin® C II

methylphenidate HCl tablets, USP
(5 mg, 10 mg, and 20 mg)
Rx only

DESCRIPTION

Methylphenidate hydrochloride is a mild central nervous system (CNS) stimulant, available as tablets of 5, 10, and 20 mg for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate Hydrochloride

$C_{14}H_{19}NO_2 \bullet HCl$ MW= 269.77

Methylphenidate Hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Each tablet, for oral administration, contains 5 mg, 10 mg, or 20 mg of methylphenidate hydrochloride. In addition, each tablet contains the following inactive ingredients: Lactose Monohydrate NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, and Talc USP.

CLINICAL PHARMACOLOGY

Methylin® is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but Methylin® presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

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

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Methylin® is 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 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.

Special Diagnostic Considerations

Specific etiology of this syndrome 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.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Methylin®, since the drug may aggravate these symptoms. Methylin® is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Methylin® is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Methylin® should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Methylin® in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Methylin® should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Methylin® should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Methylin® has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Methylin®, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Methylin® may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Methylin®.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systemically evaluated.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. However, in a recently conducted study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. In rats, teratogenic effects were not seen when the drug was given in doses of 75 mg/kg/day, which is approximately 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. Therefore, until more information is available, Methylin® should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Methylin® should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Methylin® 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 Methylin® is usually not indicated.

Long-term effects of Methylin® in children have not been well established.

Carcinogenesis/Mutagenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

Children (6 years and over)

Methylin® should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Methylin® should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

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

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate before performing gastric lavage. Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Methylin® overdosage has not been established.

HOW SUPPLIED

Each Methylin® (methylphenidate HCl tablet, USP) 5 mg is available as a round, white unscored tablet debossed with 5 on one side and a M on the other side.
Bottles of 100 .....NDC 0406-1121-01
Bottles of 1000 .....NDC 0406-1121-10

Each Methylin® (methylphenidate HCl tablet, USP) 10 mg is available as a round, white scored tablet debossed with 10 on one side of the tablet and a M on the other side.
Bottles of 100 .....NDC 0406-1122-01
Bottles of 1000 .....NDC 0406-1122-10

Each Methylin® (methylphenidate HCl tablet, USP) 20 mg is available as a round, white scored tablet debossed with 20 on one side of the tablet and a M on the other side.
Bottles of 100 .....NDC 0406-1124-01
Bottles of 1000 .....NDC 0406-1124-10

Protect from light. Dispense in tight, light-resistant container with child-resistant closure.
Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F) [see USP]. Protect from moisture.

Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.

Printed in U.S.A.
MG #14234

Rev. 123002

tyco Healthcare

Mallinckrodt

11211202
Methylin® C II
methylphenidate
HCl tablets, USP
(5 mg, 10 mg, and 20 mg)
Rx only

PV 5310 AMP

STRATTERA®
(atomoxetine HCl)

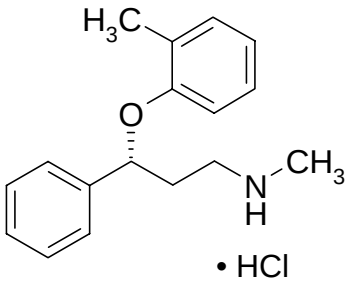
WARNING

Suicidal Ideation in Children and Adolescents — STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use).

DESCRIPTION

STRATTERA® (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO$•HCl, which corresponds to a molecular weight of 291.82. The chemical structure is:



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

STRATTERA capsules are intended for oral administration only.

Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to

selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Human Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and adolescents in selected clinical trials, primarily using population pharmacokinetic studies. Single-dose and steady-state individual pharmacokinetic data were also obtained in children, adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max}, and AUC values were observed in children, adolescents, and adults. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption and distribution — Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (C_{max}) are reached approximately 1 to 2 hours after dosing.

STRATTERA can be administered with or without food. Administration of STRATTERA with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max}, and delayed T_{max} by 3 hours. In clinical trials with children and adolescents, administration of STRATTERA with food resulted in a 9% lower C_{max}.

The steady-state volume of distribution after intravenous administration is 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. Volume of distribution is similar across the patient weight range after normalizing for body weight.

At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism and elimination — Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (*see* Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.

The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).

Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the dose). Only a small fraction of the STRATTERA dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic insufficiency — Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Renal insufficiency — EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.

Geriatric — The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population.

Pediatric — The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Gender — Gender did not influence atomoxetine disposition.

Ethnic origin — Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

Drug-Drug Interactions

CYP2D6 activity and atomoxetine plasma concentration — Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug-Drug Interactions *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Effect of atomoxetine on P450 enzymes — Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

Albuterol — Albuterol (600 mcg iv over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (*see* Drug-Drug Interactions *under* PRECAUTIONS).

Alcohol — Consumption of ethanol with STRATTERA did not change the intoxicating effects of ethanol.

Desipramine — Coadministration of STRATTERA (40 or 60 mg BID for 13 days) with desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs metabolized by CYP2D6.

Methylphenidate — Coadministration of methylphenidate with STRATTERA did not increase cardiovascular effects beyond those seen with methylphenidate alone.

Midazolam — Coadministration of STRATTERA (60 mg BID for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs (single dose of 5 mg), resulted in 15% increase in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.

Drugs highly bound to plasma protein — In vitro drug-displacement studies were conducted with atomoxetine and other highly-bound drugs at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

Drugs that affect gastric pH — Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on STRATTERA bioavailability.

CLINICAL STUDIES

The effectiveness of STRATTERA in the treatment of ADHD was established in 6 randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (*see* INDICATIONS AND USAGE).

Children and Adolescents

The effectiveness of STRATTERA in the treatment of ADHD was established in 4 randomized, double-blind, placebo-controlled studies of pediatric patients (ages 6 to 18). Approximately one-third of the patients met DSM-IV criteria for inattentive subtype and two-thirds met criteria for both inattentive and hyperactive/impulsive subtypes (*see* INDICATIONS AND USAGE).

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for STRATTERA- and placebo-treated patients using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV.

In Study 1, an 8-week randomized, double-blind, placebo-controlled, dose-response, acute treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed dose of STRATTERA (0.5, 1.2, or 1.8 mg/kg/day) or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening. At the 2 higher doses, improvements in ADHD symptoms were statistically significantly superior in STRATTERA-treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The 1.8-mg/kg/day STRATTERA dose did not provide any additional benefit over that observed with the 1.2-mg/kg/day dose. The 0.5-mg/kg/day STRATTERA dose was not superior to placebo.

In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study of children and adolescents aged 6 to 16 (N=171), patients received either STRATTERA or placebo. STRATTERA was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response, up to a maximum dose of 1.5 mg/kg/day. The mean final dose of STRATTERA was approximately 1.3 mg/kg/day. ADHD symptoms were statistically significantly improved on STRATTERA compared with placebo, as measured

on the ADHDRS scale. This study shows that STRATTERA is effective when administered once daily in the morning.

In 2 identical, 9-week, acute, randomized, double-blind, placebo-controlled studies of children aged 7 to 13 (Study 3, N=147; Study 4, N=144), STRATTERA and methylphenidate were compared with placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical response. The maximum recommended STRATTERA dose was 2.0 mg/kg/day. The mean final dose of STRATTERA for both studies was approximately 1.6 mg/kg/day. In both studies, ADHD symptoms statistically significantly improved more on STRATTERA than on placebo, as measured on the ADHDRS scale.

Examination of population subsets based on gender and age (<12 and 12 to 17) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

Adults

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 randomized, double-blind, placebo-controlled clinical studies of adult patients, age 18 and older, who met DSM-IV criteria for ADHD.

Signs and symptoms of ADHD were evaluated using the investigator-administered Conners Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary effectiveness measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales from the CAARS) evaluated by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis.

In 2 identical, 10-week, randomized, double-blind, placebo-controlled acute treatment studies (Study 5, N=280; Study 6, N=256), patients received either STRATTERA or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response in a range of 60 to 120 mg/day. The mean final dose of STRATTERA for both studies was approximately 95 mg/day. In both studies, ADHD symptoms were statistically significantly improved on STRATTERA, as measured on the ADHD Symptom score from the CAARS scale.

Examination of population subsets based on gender and age (<42 and ≥42) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

INDICATIONS AND USAGE

STRATTERA is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 placebo-controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2 placebo-controlled trials in adults who met DSM-IV criteria for ADHD (*see* CLINICAL STUDIES).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause 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 also 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

STRATTERA is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, 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 effectiveness of STRATTERA for long-term use, i.e., for more than 9 weeks in child and adolescent patients and 10 weeks in adult patients, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity

STRATTERA is contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product (*see* WARNINGS).

Monoamine Oxidase Inhibitors (MAOI)

STRATTERA should not be taken with an MAOI, or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing STRATTERA. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.

Narrow Angle Glaucoma

In clinical trials, STRATTERA use was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

WARNINGS

Suicidal Ideation

STRATTERA increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving STRATTERA and 851 receiving placebo). The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with STRATTERA. **No suicides occurred in these trials.** All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with STRATTERA for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of STRATTERA.

All pediatric patients being treated with STRATTERA should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes. Such monitoring would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

The following symptoms have been reported with STRATTERA: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the emergence of suicidal impulses has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality. Thus, patients being treated with STRATTERA should be observed for the emergence of such symptoms.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who are experiencing emergent suicidality or symptoms that might be precursors to emerging suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with STRATTERA should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder — In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with STRATTERA, 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.

Severe Liver Injury

Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about

6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that STRATTERA caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury, and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant.

STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). (*See also* Information for Patients *under* PRECAUTIONS.)

Allergic Events

Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported in patients taking STRATTERA.

PRECAUTIONS

General

Effects on blood pressure and heart rate — STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following STRATTERA dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute, compared with 0.5% (1/204) of placebo subjects. No pediatric subject had a heart rate increase of at least 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion. Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients 10.4 beats/minute.

STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of STRATTERA-treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of STRATTERA-treated subjects and 1.5% (3/200) of placebo subjects. (High systolic and diastolic blood pressure measurements were defined as those exceeding the 95th percentile, stratified by

age, gender, and height percentile - National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.)

In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of 5 beats/minute compared with placebo subjects. Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.

STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pressure measurements ≥150 mm Hg compared with 1.2% (3/256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements ≥100 mm Hg compared with 0.4% (1/257) of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on more than one occasion.

Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term, child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated subjects. STRATTERA should be used with caution in any condition that may predispose patients to hypotension.

Effects on urine outflow from the bladder — In adult ADHD controlled trials, the rates of urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among atomoxetine subjects compared with placebo subjects (0%, 0/263). Two adult atomoxetine subjects and no placebo subjects discontinued from controlled clinical trials because of urinary retention. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Effects on Growth — Data on the long-term effects of STRATTERA on growth come from open-label studies, and weight and height changes are compared to normative population data. In general, the weight and height gain of pediatric patients treated with STRATTERA lags behind that predicted by normative population data for about the first 9-12 months of treatment. Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with STRATTERA have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data. After about 12 months, gain in height stabilizes, and at 3 years, patients treated with STRATTERA have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data (*see* Figure 1 below).

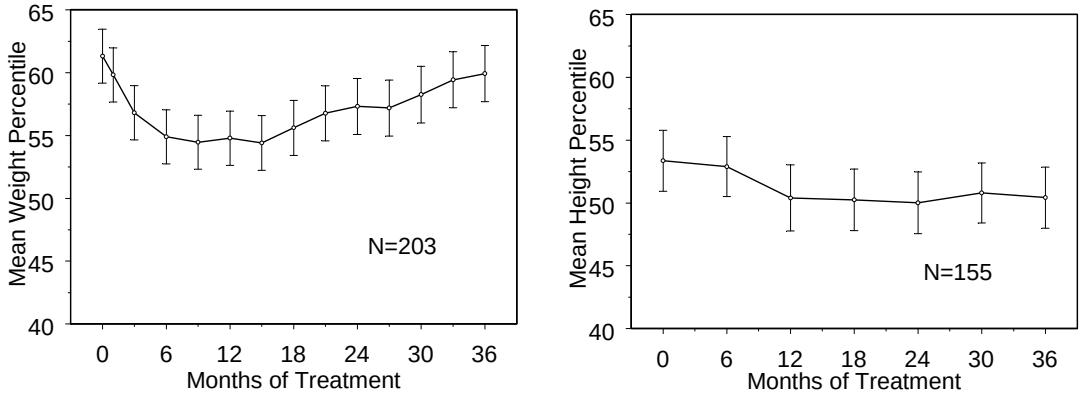


Figure 1: Mean Weight and Height Percentiles Over Time for Patients With Three Years of STRATTERA Treatment

This growth pattern was generally similar regardless of pubertal status at the time of treatment initiation. Patients who were pre-pubertal at the start of treatment (girls ≤8 years old, boys ≤9 years old) gained an average of 2.1 kg and 1.2 cm less than predicted after three years. Patients who were pubertal (girls >8 to ≤13 years old, boys >9 to ≤14 years old) or late pubertal (girls >13 years old, boys >14 years old) had average weight and height gains that were close to or exceeded those predicted after three years of treatment.

Growth followed a similar pattern in both extensive and poor metabolizers (EMs, PMs). PMs treated for at least two years gained an average of 2.4 kg and 1.1 cm less than predicted, while EMs gained an average of 0.2 kg and 0.4 cm less than predicted.

In short-term controlled studies (up to 9 weeks), STRATTERA-treated patients lost an average of 0.4 kg and gained an average of 0.9 cm, compared to a gain of 1.5 kg and 1.1 cm in the placebo-treated patients. In a fixed-dose controlled trial, 1.3%, 7.1%, 19.3%, and 29.1% of patients lost at least 3.5% of their body weight in the placebo, 0.5, 1.2, and 1.8 mg/kg/day dose groups.

Growth should be monitored during treatment with STRATTERA.

Aggressive Behavior or Hostility — 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 conclusive evidence that STRATTERA causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with STRATTERA compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Information for Patients

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

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking STRATTERA.

Suicide Risk — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, depression, and suicidal ideation, especially early during STRATTERA treatment and when the dose is adjusted. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients initiating STRATTERA should be cautioned that liver dysfunction may develop rarely. Patients should be instructed to contact their physician immediately should they develop pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms.

Patients should be instructed to call their doctor as soon as possible should they notice an increase in aggression or hostility.

STRATTERA is an ocular irritant. STRATTERA capsules are not intended to be opened. In the event of capsule content coming in contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Patients should consult a physician if they are taking or plan to take any prescription or over-the-counter medicines, dietary supplements, or herbal remedies.

Patients should consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking STRATTERA.

Patients may take STRATTERA with or without food.

If patients miss a dose, they should take it as soon as possible, but should not take more than the prescribed total daily amount of STRATTERA in any 24-hour period.

Patients should use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

Laboratory Tests

Routine laboratory tests are not required.

CYP2D6 metabolism — Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (*see* ADVERSE REACTIONS).

Drug-Drug Interactions

Albuterol — STRATTERA should be administered with caution to patients being treated with systemically-administered (oral or intravenous) albuterol (or other $beta_2$ agonists) because the action of albuterol on the cardiovascular system can be potentiated resulting in increases in heart rate and blood pressure.

CYP2D6 inhibitors — Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, selective inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* DOSAGE AND ADMINISTRATION). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Pressor agents — Because of possible effects on blood pressure, STRATTERA should be used cautiously with pressor agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Atomoxetine HCl was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The highest dose used in rats is approximately 8 and 5 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis. Plasma levels (AUC) of atomoxetine at this dose in rats are estimated to be 1.8 times (extensive metabolizers) or 0.2 times (poor metabolizers) those in humans receiving the maximum human dose. The highest dose used in mice is approximately

39 and 26 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis.

Mutagenesis — Atomoxetine HCl was negative in a battery of genotoxicity studies that included a reverse point mutation assay (Ames Test), an in vitro mouse lymphoma assay, a chromosomal aberration test in Chinese hamster ovary cells, an unscheduled DNA synthesis test in rat hepatocytes, and an in vivo micronucleus test in mice. However, there was a slight increase in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting endoreduplication (numerical aberration).

The metabolite N-desmethylatomoxetine HCl was negative in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

Impairment of fertility — Atomoxetine HCl did not impair fertility in rats when given in the diet at doses of up to 57 mg/kg/day, which is approximately 6 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C — Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100-mg/kg dose is approximately 23 times the maximum human dose on a mg/m^2 basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maximum human dose.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the maximum human dose on a mg/m^2 basis) in the diet from 2 weeks (females) or 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The decreased pup survival was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which rats were treated with atomoxetine in the diet from 2 weeks (females) or 10 weeks (males) prior to mating throughout the period of organogenesis, a decrease in fetal weight (female only) and an increase in the incidence of incomplete ossification of the vertebral arch in fetuses were observed at 40 mg/kg/day (approximately 5 times the maximum human dose on a mg/m^2 basis) but not at 20 mg/kg/day.

No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (approximately 17 times the maximum human dose on a mg/m^2 basis) by gavage throughout the period of organogenesis.

No adequate and well-controlled studies have been conducted in pregnant women. STRATTERA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Parturition in rats was not affected by atomoxetine. The effect of STRATTERA on labor and delivery in humans is unknown.

Nursing Mothers

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if STRATTERA is administered to a nursing woman.

Pediatric Use

Anyone considering the use of STRATTERA in a child or adolescent must balance the potential risks with the clinical need (*see* BOX WARNING *and* WARNINGS, Suicidal Ideation).

The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not been established. The efficacy of STRATTERA beyond 9 weeks and safety of STRATTERA beyond 1 year of treatment have not been systematically evaluated.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day (approximately 0.2, 2, and 8 times, respectively, the maximum human dose on a mg/m^2 basis) of atomoxetine given by gavage from the early postnatal period (Day 10 of age) through adulthood. Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg), slight decreases in epididymal weight and sperm number (10 and 50 mg/kg), and a slight decrease in corpora lutea (50 mg/kg) were seen, but there were no effects on fertility or reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A slight increase in motor activity was seen on Day 15 (males at 10 and 50 mg/kg and females at 50 mg/kg) and on Day 30 (females at 50 mg/kg) but not on Day 60 of age. There were no effects on learning and memory tests. The significance of these findings to humans is unknown.

Geriatric Use

The safety and efficacy of STRATTERA in geriatric patients have not been established.

ADVERSE REACTIONS

STRATTERA was administered to 2067 children or adolescent patients with ADHD and 270 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 patients were treated for longer than 1 year and 526 patients were treated for over 6 months.

The data in the following tables and text cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. The cited data provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

Child and Adolescent Clinical Trials

Reasons for discontinuation of treatment due to adverse events in child and adolescent clinical trials — In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7% of poor metabolizer (PM) patients discontinued because of an adverse event. Among STRATTERA-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); somnolence (0.5%, N=2); and vomiting (0.5%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly observed adverse events in acute child and adolescent, placebo-controlled trials — Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 1 for the BID trials. Results were similar in the QD trial except as shown in Table 2, which shows both BID and QD results for selected adverse events. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients, for either BID or QD dosing) were: dyspepsia, nausea, vomiting, fatigue, appetite decreased, dizziness, and mood swings (*see* Tables 1 *and* 2).

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials		
Adverse Event[1]	Percentage of Patients Reporting Events from BID Trials	
	STRATTERA (N=340)	Placebo (N=207)
Gastrointestinal Disorders		
Abdominal pain upper	20	16
Constipation	3	1
Dyspepsia	4	2
Vomiting	11	9
Infections		
Ear infection	3	1
Influenza	3	1
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness (exc vertigo)	6	3
Headache	27	25
Somnolence	7	5
Psychiatric Disorders		
Crying	2	1
Irritability	8	5
Mood swings	2	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	11	7
Rhinorrhea	4	3
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials				
Adverse Event	Percentage of Patients Reporting Events from BID Trials		Percentage of Patients Reporting Events from QD Trials	
	STRATTERA (N=340)	Placebo (N=207)	STRATTERA (N=85)	Placebo (N=85)
Gastrointestinal Disorders				
Abdominal pain upper	20	16	16	9
Constipation	3	1	0	0
Diarrhea	3	6	4	1
Dry mouth	1	2	4	1
Dyspepsia	4	2	8	0
Nausea	7	8	12	2
Vomiting	11	9	15	1
General Disorders				
Fatigue	4	5	9	1
Psychiatric Disorders				
Mood swings	2	0	5	2

The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistically significantly more frequent in PM patients compared with EM patients: decreased appetite (23% of PMs, 16% of EMs); insomnia (13% of PMs, 7% of EMs); sedation (4% of PMs, 2% of EMs); depression (6% of PMs, 2% of EMs); tremor (4% of PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs).

Adult Clinical Trials

Reasons for discontinuation of treatment due to adverse events in acute adult placebo-controlled trials — In the acute adult placebo-controlled trials, 8.5% (23/270) atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for adverse events. Among STRATTERA-treated patients, insomnia (1.1%, N=3); chest pain (0.7%, N=2); palpitations (0.7%, N=2); and urinary retention (0.7%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly observed adverse events in acute adult placebo-controlled trials — Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 3. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients) were: constipation, dry mouth, nausea, appetite decreased, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea (*see* Table 3).

Table 3: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 10 weeks) Adult Trials		
Adverse Event[1]	Percentage of Patients Reporting Event	
System Organ Class/Adverse Event	STRATTERA (N=269)	Placebo (N=263)
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
General Disorders and Administration Site Conditions		
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Infections		
Sinusitis	6	4
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	16	8
Paraesthesia	4	2
Sinus headache	3	1
Psychiatric Disorders		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8	0
Reproductive System and Breast Disorders		
Dysmenorrhea[3]	7	3
Ejaculation failure[2] and/or ejaculation disorder[2]	5	2
Erectile disturbance[2]	7	1
Impotence[2]	3	0

Menses delayed[3]	2	1
Menstrual disorder[3]	3	2
Menstruation irregular[3]	2	0
Orgasm abnormal	2	1
Prostatitis[2]	3	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: early morning awakening, peripheral coldness, tachycardia. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: abdominal pain upper, arthralgia, back pain, cough, diarrhea, influenza, irritability, nasopharyngitis, sore throat, upper respiratory tract infection, vomiting.
[2] Based on total number of males (STRATTERA, N=174; placebo, N=172).
[3] Based on total number of females (STRATTERA, N=95; placebo, N=91).

Male and female sexual dysfunction — Atomoxetine appears to impair sexual function in some patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well assessed in most clinical trials because they need special attention and because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate the actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of adult patients taking STRATTERA in placebo-controlled trials.

Table 4

	STRATTERA	Placebo
Erectile disturbance[1]	7%	1%
Impotence[1]	3%	0%
Orgasm abnormal	2%	1%

[1] Males only.

There are no adequate and well-controlled studies examining sexual dysfunction with STRATTERA treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of STRATTERA, physicians should routinely inquire about such possible side effects.

Postmarketing Spontaneous Reports

The following list of undesirable effects (adverse drug reactions) is based on post-marketing spontaneous reports, and corresponding reporting rates have been provided.

Vascular disorders — *Very rare (<0.01%):* Peripheral vascular instability and/or Raynaud's phenomenon (new onset and exacerbation of preexisting condition).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

STRATTERA is not a controlled substance.

Physical and Psychological Dependence

In a randomized, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of STRATTERA and placebo, STRATTERA was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with STRATTERA. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

Animal Experience

Drug discrimination studies in rats and monkeys showed inconsistent stimulus generalization between atomoxetine and cocaine.

OVERDOSAGE

Human Experience

There is limited clinical trial experience with STRATTERA overdose and no fatalities were observed. During postmarketing, there have been reports of acute and chronic overdoses of STRATTERA. No fatal overdoses of STRATTERA alone have been reported. The most commonly reported symptoms accompanying acute and chronic overdoses were somnolence, agitation, hyperactivity, abnormal behavior, and gastrointestinal symptoms. Signs and symptoms consistent with sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth) have also been observed.

Management of Overdose

An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosing of children and adolescents up to 70 kg body weight — STRATTERA should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (*see* CLINICAL STUDIES).

The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

Dosing of children and adolescents over 70 kg body weight and adults — STRATTERA should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses (*see* CLINICAL STUDIES).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with STRATTERA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

STRATTERA may be taken with or without food.

The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Dosing adjustment for hepatically impaired patients — For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal (*see* Special Populations *under* CLINICAL PHARMACOLOGY).

Dosing adjustment for use with a strong CYP2D6 inhibitor — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atomoxetine can be discontinued without being tapered.

Instructions for Use/Handling

STRATTERA capsules are not intended to be opened, they should be taken whole. (*See also* Information for Patients *under* PRECAUTIONS.)

HOW SUPPLIED

STRATTERA® (atomoxetine HCl) capsules are supplied in 10-, 18-, 25-, 40-, 60-, 80-, and 100-mg strengths.

STRATTERA® Capsules	**10 mg***	**18 mg***	**25 mg***	**40 mg***	**60 mg***	**80 mg***	**100 mg***
Color	Opaque White, Opaque White	Gold, Opaque White	Opaque Blue, Opaque White	Opaque Blue, Opaque Blue	Opaque Blue, Gold	Opaque Brown, Opaque White	Opaque Brown, Opaque Brown
Identification	LILLY 3227 10 mg	LILLY 3238 18 mg	LILLY 3228 25 mg	LILLY 3229 40 mg	LILLY 3239 60 mg	LILLY 3250 80 mg	LILLY 3251 100 mg
NDC Codes:							

Bottles of 30	0002-3227-30	0002-3238-30	0002-3228-30	0002-3229-30	0002-3239-30	0002-3250-30	0002-3251-30
Bottles of 1500							0002-3251-49
Bottles of 2000	0002-3227-07	0002-3238-07	0002-3228-07	0002-3229-07	0002-3239-07	0002-3250-07	

* Atomoxetine base equivalent.

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

Medication Guide

STRATTERA®

Generic name: atomoxetine hydrochloride

Read this information carefully before you start taking STRATTERA (Stra-TAIR-a) to learn about the benefits and risks of STRATTERA. Read the information you get with STRATTERA each time you get more STRATTERA, as there may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

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

Parents or guardians need to think about 4 important things when their child/teenager is prescribed STRATTERA:

1. There is a risk of suicidal thinking
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking STRATTERA
4. There are benefits and risks when using STRATTERA

1. There is a Risk of Suicidal Thinking

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

STRATTERA increased suicidal thinking in some children being treated for ADHD in clinical trials.

A large study combined the results of 12 different studies of children and teenagers with ADHD. In these studies, patients took either a placebo (sugar pill) or STRATTERA for 6 to 18 weeks. ***No one committed suicide in these studies,*** but some patients experienced suicidal thinking. On sugar pills, no patients developed suicidal thinking. On STRATTERA, 4 out of every 1000 patients developed suicidal thinking.

For some children and teenagers, the risks of suicidal thinking or behaviors may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes STRATTERA.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, talk with and listen to your child about his or her thoughts and feelings and pay close attention to changes in his or her moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3.

Whenever STRATTERA is started or its dose is changed, pay close attention to your child.

After starting STRATTERA, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking STRATTERA for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (*see* Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking STRATTERA

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior

4. There are Benefits and Risks When Using STRATTERA

STRATTERA is a non-stimulant medicine used to treat Attention-Deficit/Hyperactivity Disorder (ADHD). In some children and teenagers who participated in clinical trials, treatment with STRATTERA increased suicidal thinking. It is important to discuss all the risks of treating

ADHD and also the risks of not treating it. As with all treatments for ADHD, you should discuss with your healthcare provider the potential benefits and risks of STRATTERA.

What is STRATTERA?

STRATTERA is a non-stimulant medicine used to treat ADHD in children, teenagers and adults. STRATTERA contains atomoxetine hydrochloride, a selective norepinephrine reuptake inhibitor. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD.

What is ADHD?

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all 3 types of symptoms.

Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, daytime drowsiness, slow processing of information, difficulty learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low self-esteem, and excessive effort to maintain some organization. The symptoms shown by adults who primarily have attention problems but not hyperactivity have been commonly described as Attention-Deficit Disorder (ADD).

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

Who should NOT take STRATTERA?

Do not take STRATTERA if:

- you took a medicine known as a monoamine oxidase inhibitor (MAOI) in the last 2 weeks. An MAOI is a medicine sometimes used for depression and other mental problems. Some names of MAOI medicines are Nardil® (phenelzine sulfate) and Parnate® (tranylcypromine sulfate). Taking STRATTERA with an MAOI could cause serious side effects or be life-threatening.
- you have an eye disease called narrow angle glaucoma.
- you are allergic to STRATTERA or any of its ingredients. The active ingredient is atomoxetine. The inactive ingredients are listed at the end of this Medication Guide.

What should I tell my doctor before taking STRATTERA?

Talk to your doctor before taking STRATTERA if you:

- have or had suicidal thoughts.
- have or had liver problems. You may need a lower dose.
- have high blood pressure. STRATTERA can increase blood pressure.

- have problems with your heart or an irregular heartbeat. STRATTERA can increase heart rate (pulse).
- have low blood pressure. STRATTERA can cause dizziness or fainting in people with low blood pressure.

Tell your doctor about all the medicines you take or plan to take, including prescription and non-prescription medicines, dietary supplements, and herbal remedies. Your doctor will decide if you can take STRATTERA with your other medicines.

Certain medicines may change the way your body reacts to STRATTERA. These include medicines used to treat depression [like Paxil® (paroxetine hydrochloride) and Prozac® (fluoxetine hydrochloride)], and certain other medicines (like quinidine). Your doctor may need to change your dose of STRATTERA if you are taking it with these medicines.

STRATTERA may change the way your body reacts to oral or intravenous albuterol (or drugs with similar actions), but the effectiveness of these drugs will not be changed. Talk with your doctor before taking STRATTERA if you are taking albuterol.

How should I take STRATTERA?

- Take STRATTERA according to your doctor's instructions. This is usually taken 1 or 2 times a day (morning and late afternoon/early evening).
- You can take STRATTERA with or without food.
- If you miss a dose, take it as soon as possible, but do not take more than your total daily dose in any 24-hour period.
- Taking STRATTERA at the same time each day may help you remember.
- STRATTERA is available in several dosage strengths: 10, 18, 25, 40, 60, 80, and 100 mg.

Call your doctor right away if you take more than your prescribed dose of STRATTERA.

You should not open STRATTERA capsules, but if they are accidentally opened or broken you should avoid contact with the powder and wash away any loose powder as soon as possible with water. If any of the powder gets in your eyes you should rinse them with water immediately and contact your doctor.

Other important safety information about STRATTERA

STRATTERA can cause liver damage in rare cases. Call your doctor right away if you have itching, dark urine, yellow skin/eyes, upper right-sided abdominal tenderness, or unexplained "flu-like" symptoms.

Use caution when driving a car or operating heavy machinery until you know how STRATTERA affects you.

If you notice an increase in aggression or hostility since taking this medication, you should call your doctor as soon as possible.

Talk to your doctor if you are:

- pregnant or planning to become pregnant

- breast-feeding. We do not know if STRATTERA can pass into your breast milk.

What are the common side effects of STRATTERA?

The most common side effects of STRATTERA used in teenagers and children over 6 years old are:

- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness
- tiredness
- mood swings

Weight loss may occur after starting STRATTERA. Treatment data up to 3 years indicates minimal, if any, long-term effects of STRATTERA on weight and height. Your doctor will watch your weight and height. If you are not growing or gaining weight as expected, your doctor may change your treatment with STRATTERA.

The most common side effects of STRATTERA used in adults are:

- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- problems sleeping
- sexual side effects
- problems urinating
- menstrual cramps

Stop taking STRATTERA and call your doctor right away if you get swelling or hives. STRATTERA can cause a serious allergic reaction in rare cases.

This is not a complete list of side effects. Talk to your doctor if you develop any symptoms that concern you.

See also “What is the most important information I should know about STRATTERA?” *and* “Other important safety information about STRATTERA”.

General advice about STRATTERA

STRATTERA has not been studied in children under 6 years old.

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use STRATTERA for a condition for which it was not prescribed. Do not give STRATTERA to other people, even if they have the same symptoms you have.

This Medication Guide summarizes the most important information about STRATTERA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information on STRATTERA that is written for health professionals. You can also call 1-800-Lilly-Rx (1-800-545-5979) or visit our website at www.strattera.com.

What are the ingredients in STRATTERA?

Active ingredient: atomoxetine.

Inactive ingredients: pregelatinized starch, dimethicone, gelatin, sodium lauryl sulfate, FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide, and edible black ink.

Store STRATTERA at room temperature.

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

Literature revised November 8, 2005

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