

Dr. Rosenbloom
A pioneer in pediatric endocrinology,

Arlan L. Rosenbloom, M.D., FAAP, of Gainesville, Fla., will receive the 2003 Distinguished Physician Award from the Endocrine Society for outstanding contributions to clinical endocrinology.

Dr. Rosenbloom is Distinguished Service Professor Emeritus of Pediatrics at University of Florida College of Medicine. He founded the university's Division of Pediatric Endocrinology, the state-funded Regional Diabetes and Endocrine Program for Children and Florida's Camps for Children and Youth with Diabetes.

Dr. Rosenbloom is medical director for Florida's Children's Medical Services Program, the Title V case management

system for children with special health care needs.



Dr. Roth

He is a member of the AAP Section on Seniors.

Trisha Roth, M.D., FAAP, of West Los Angeles, Calif., received the Susan Laufer Award from SHARE! (Self-Help

and Recovery Exchange) for her efforts in community self-help groups and in fighting substance abuse.

Dr. Roth, assistant clinical professor at UCLA, is in private practice. She was the liaison from the American Society of Addiction Medicine to the 2002 National Leadership Conference of the American Medical Association Women Physicians' Summit.



Dr. Schwartz

Dr. Schwartz, director of pediatric ophthalmology and strabismus,

and professor of ophthalmology and pediatrics at WVU, convinced ophthalmologists throughout the state to donate office space for evaluation and treatment of children with low vision, formed parental support groups for the families, established lending libraries of low vision devices and educational materials and obtained private donations to fund the projects.

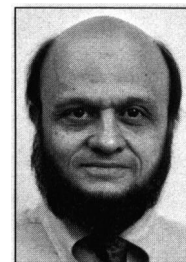
A consulting ophthalmologist to the West Virginia Schools for the Deaf and the Blind, Dr. Schwartz is a member of the AAP Section on Ophthalmology.

Terry Schwartz, M.D., FAAP, of Morgantown, W.V., received the West Virginia University (WVU) Dean's Award of Excellence for Community Service for her efforts serving children with low vision.

Dr. Schwartz, director of pediatric ophthalmology and strabismus, and professor of ophthalmology and pediatrics at WVU, convinced ophthalmologists throughout the state to donate office space for evaluation and treatment of children with low vision, formed parental support groups for the families, established lending libraries of low vision devices and educational materials and obtained private donations to fund the projects.

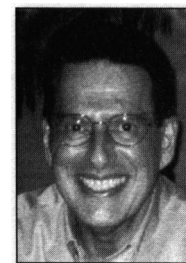
A consulting ophthalmologist to the West Virginia Schools for the Deaf and the Blind, Dr. Schwartz is a member of the AAP Section on Ophthalmology.

IN MEMORIAM



Dr. Kirschner

Robert H. Kirschner, M.D., FAAP, of Chicago, died of complications from cancer Sept. 15 at age 61.



Dr. Melam

Howard L. Melam, M.D., FAAP, of Schaumburg, Ill., died of cancer June 7 at age 61.

Russell Nelson, M.D., FAAP, of Wichita, Kans., died of prostate cancer Sept. 12 at age 83.

Mildred J. Polniaszek, M.D., FAAP, of Lincolnwood, Ill., died of cancer Aug. 25 at age 82.

George W. Prather, M.D., FAAP, of Opelousas, La., died Sept. 8 at age 81.

Ira M. Rosenthal, M.D., FAAP, of Chicago, died of complications from an infection Sept. 18 at age 82.

Sheila M. Tunnell, M.D., FAAP, of Aurora, Colo., died Sept. 1 at age 62.

Ritalin® LA (methylphenidate hydrochloride) extended-release capsules

Rx only
BRIEF SUMMARY: Please see package insert for full prescribing information.

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 in the full prescribing information). 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 in the full prescribing information).

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 parental 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 co-administration 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/m² 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/m² basis, respectively. In a 24-week carcinogenicity study in the transgenic mouse strain T533+, 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 5-fold the highest recommended dose on a mg/kg and mg/m² 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/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m² 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 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	Placebo N=71
	N (%)	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 (6/61, 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. **Hepato-Biliary:** 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.)

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

Manufactured for:
Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936
By ELAN HOLDINGS INC., Pharmaceutical Division, Gainesville, GA 30504

JUNE 2002
©2002 Novartis
PRINTED IN U.S.A.

T2002-28
89015701



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

©2002 Novartis

Printed in U.S.A.

8/02

C-RLA-1003

Printed on Recycled Paper