NOVARTIS

T2007-21

Focalin®

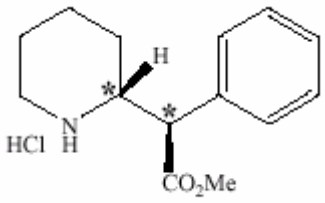
dexmethylphenidate hydrochloride tablets C II

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 $1_{1}/_{2}$ 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 similar for boys and girls (mean age 10 years).

In a single dose study conducted in adults, the mean dexmethylphenidate $AUC_{0\text{-}inf}$ 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®*

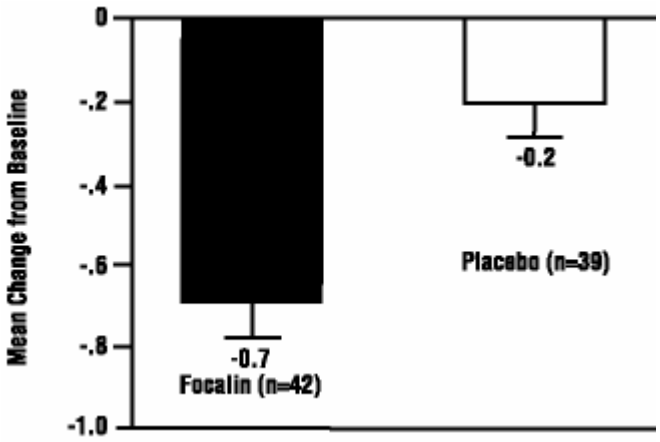
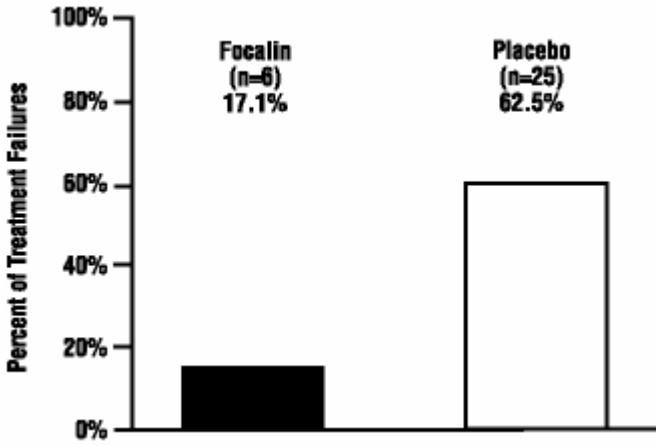


*Figure 1: Error bars represent the standard error of the mean.

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

Serious Cardiovascular Events

Sudden Death and Pre-Existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-Existing Psychosis

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

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow- up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children

over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

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

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with dexmethylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for

Focalin. 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.

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 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.

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).

In a study conducted in young rats, racemic 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] of racemic methylphenidate 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 racemic MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

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 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 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, tachycardia

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, aggressive behavior

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.

MEDICATION GUIDE

FOCALIN®

(dexmethylphenidate hydrochloride tablets) CII

Read the Medication Guide that comes with FOCALIN® before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with FOCALIN®.

What is the most important information I should know about FOCALIN®?

The following have been reported with use of dexmethylphenidate hydrochloride and other stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting FOCALIN®.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with FOCALIN®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking FOCALIN®.

2. Mental (Psychiatric) problems:

All Patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers

- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking FOCALIN®, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What Is FOCALIN®?

FOCALIN® is a central nervous system stimulant prescription medicine. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD).** FOCALIN® may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

FOCALIN® should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

FOCALIN® is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep FOCALIN® in a safe place to prevent misuse and abuse. Selling or giving away FOCALIN® may harm others, and is against the law.

Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take FOCALIN®?

FOCALIN® should not be taken if you or your child:

- are very anxious, tense, or agitated
- have an eye problem called glaucoma
- have tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard to control repeated movements or sounds.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- are allergic to anything in FOCALIN®. See the end of this Medication Guide for a complete list of ingredients.

FOCALIN® should not be used in children less than 6 years old because it has not been studied in this age group.

FOCALIN® may not be right for you or your child. Before starting FOCALIN® tell your or your child's doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- seizures or have had an abnormal brain wave test (EEG)

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breast-feeding.

Can FOCALIN® be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. FOCALIN® and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking FOCALIN®.

Your doctor will decide whether FOCALIN® can be taken with other medicines.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking FOCALIN® without talking to your doctor first.

How should FOCALIN® be taken?

- **Take FOCALIN exactly as prescribed**. Your doctor may adjust the dose until it is right for you or your child.
- Take FOCALIN® twice a day, at least 4 hours apart.
- FOCALIN® can be taken with or without food.
- From time to time, your doctor may stop FOCALIN® treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking FOCALIN®. Children should have their height and weight checked often while taking FOCALIN®. FOCALIN® treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much FOCALIN® or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of FOCALIN®?

See **"What is the most important information I should know about FOCALIN®?"** for information on reported heart and mental problems.

Other serious side effects include:

- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

Common side effects include:

- stomach ache
- nausea
- decreased appetite
- fever

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

How should I store FOCALIN®?

- Store FOCALIN® in a safe place at room temperature, 59 to 86° F (15 to 30° C).

- **Keep FOCALIN® and all medicines out of the reach of children.**

General information about FOCALIN®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOCALIN® for a condition for which it was not prescribed. Do not give FOCALIN® to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about FOCALIN®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOCALIN® that was written for healthcare professionals. For more information about FOCALIN® call 1-888-669-6682.

What are the ingredients in FOCALIN®?

Active Ingredient: dexmethylphenidate hydrochloride

Inactive 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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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NOVARTIS

Manufactured for:

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East Hanover, NJ 07936

By:

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NOVARTIS

T2007-22

Focalin® XR

(dexmethylphenidate hydrochloride)
extended-release capsules

Rx only

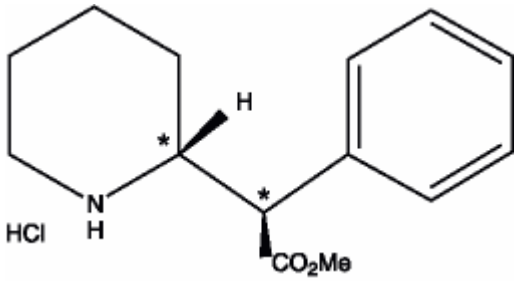
Prescribing Information

DESCRIPTION

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Focalin® XR uses the proprietary SODAS® (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Focalin XR is available as 5, 10, 15, and 20 mg extended-release capsules. Focalin XR 5, 10, 15, and 20 mg extended-release capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, 7.5 or 10 mg of Focalin® given b.i.d. as tablets.

Dexmethylphenidate hydrochloride, the *d-threo* enantiomer of racemic methylphenidate hydrochloride, is a central nervous system (CNS) stimulant.

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.

Inactive ingredients: ammonio methacrylate copolymer, FD&C Blue #2 (5 mg and 15 mg strengths), FDA/E172 yellow iron oxide (10 mg and 15 mg strengths), gelatin, ink Tan SW-8010, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide, and triethyl citrate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Dexmethylphenidate hydrochloride, the active ingredient in Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules, is a central nervous system stimulant. Dexmethylphenidate, the more pharmacologically active *d*-enantiomer of racemic 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. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

Pharmacokinetics

Absorption

Focalin XR produces a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately 4 hours apart) when orally administered to healthy adults. The initial rate of absorption for Focalin XR is similar to that of Focalin tablets as shown by the similar rate parameters between the two formulations, i.e., first peak concentration (C_{max1}), and time to the first peak (t_{max1}), which is reached in 1 ½ hours (typical range 1-4 hours). The mean time to the interpeak minimum (t_{minip}) is slightly shorter, and time to the second peak (t_{max2}) is slightly longer for Focalin XR given once daily (about 6.5 hours, range 4.5-7 hours) compared to Focalin tablets given in two doses 4 hours apart (see Figure 1), although the ranges observed are greater for Focalin XR.

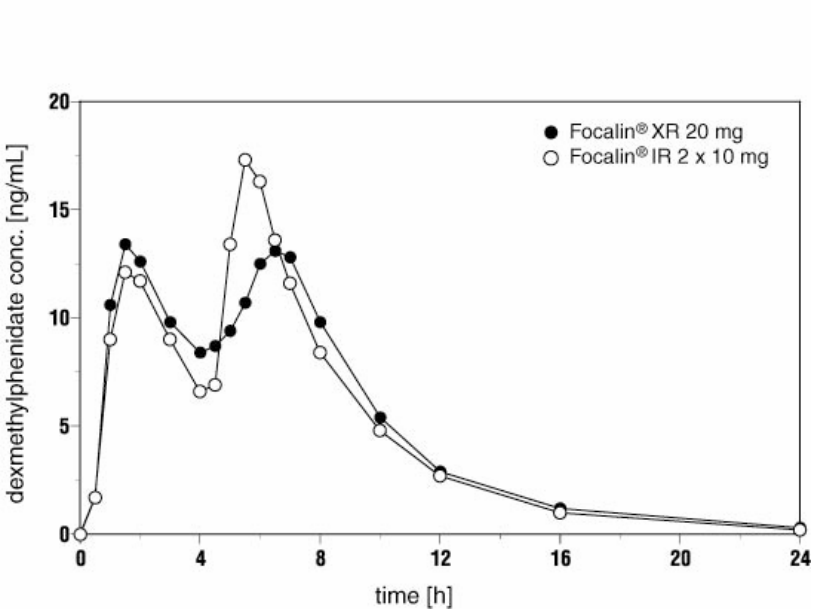
Focalin XR given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than Focalin tablets given in two doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from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

The AUC (exposure) after administration of Focalin XR given once daily is equivalent to the same total dose of Focalin tablets given in two doses 4 hours apart. The variability in

C_{max}, C_{min}, and AUC is similar between Focalin XR and Focalin IR with approximately a three-fold range in each.

Radiolabeled racemic methylphenidate is well absorbed after oral administration with approximately 90% of the radioactivity recovered in urine. However, due to first pass metabolism the mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22-25%.

Figure 1. Mean Dexmethylphenidate Plasma Concentration-Time Profiles After Administration of 1 x 20 mg Focalin® XR (n=24) Capsules and 2 x 10 mg Focalin® Immediate-Release Tablets (n=25)



Dose Proportionality

Dose proportionality of Focalin XR was evaluated in a randomized, single-dose, five-period, cross-over study with administration of single doses of 5, 10, 20, 30 and 40 mg to healthy adults. Results confirmed dose proportionality within this dose range.

Food Effects

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

No food effect study was performed with Focalin XR. However, the effect of food has been studied in adults with racemic methylphenidate in the same type of extended-release formulation. The findings of that study are considered applicable to Focalin XR. After a high fat breakfast, there was 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 is no evidence of dose dumping in the presence or absence of food. There were no differences in the plasma concentration-time profile, when administered with applesauce, compared to administration in the fasting condition. The results are expected not to differ for Focalin XR.

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

Distribution

The plasma protein binding of dexmethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12-15%, independent of concentration. Dexmethylphenidate shows a volume of distribution of 2.65±1.11 L/kg. Plasma dexmethylphenidate concentrations decline monophasically following oral administration of Focalin XR.

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 no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of no levels of *l-threo*-methylphenidate being detectable after administration of up to 40 mg dexmethylphenidate in adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic (*d,l*-) methylphenidate was *d,l*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5% of an intravenous dose.

In vitro studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes at concentrations observed after therapeutic doses.

Intravenous dexmethylphenidate was eliminated with a mean clearance of 0.40±0.12 L/kg.h^{-1} corresponding to 0.56±0.18 L/min. The mean terminal elimination half-life of dexmethylphenidate was just over 3 hours in healthy adults and typically varied between 2 and 4.5 hours with an occasional subject exhibiting a terminal half-life between 5 and 7 hours. Children tend to have slightly shorter half-lives with means of 2–3 hours.

Special Populations

Gender

After administration of Focalin XR the first peak, (C_{max1}), was on average 45% higher in women. The interpeak minimum and the second peak also tended to be slightly higher in women although the difference was not statistically significant, and these patterns remained even after weight normalization. Pharmacokinetic parameters for dexmethylphenidate after Focalin immediate-release tablets were similar for boys and girls.

Race

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

Age

The pharmacokinetics of dexmethylphenidate after Focalin XR administration have not been studied in children less than 18 years of age. When a similar formulation of racemic methylphenidate was examined in 15 children between 10 and 12 years of age and 3 children with ADHD between 7 and 9 years of age, the time to the first peak was similar, although 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 administration of the same dose to children and adults, concentrations in children were approximately twice the concentrations observed in adults. This higher exposure is almost completely due to smaller body size as no relevant age-related differences in dexmethylphenidate pharmacokinetic parameters (i.e., clearance and volume of distribution) are observed after normalization to dose and weight.

Renal Insufficiency

There is no experience with the use of Focalin XR 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 racemic ritalinic acid which is pharmacologically inactive. Very little unchanged drug is excreted in the urine, thus renal insufficiency is expected to have little effect on the pharmacokinetics of Focalin XR.

Hepatic Insufficiency

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

CLINICAL STUDIES

The effectiveness of Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules in the treatment of ADHD was established in randomized, double-blind, placebo-controlled studies in children and adolescents and in adults who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (see INDICATIONS AND USAGE).

Children and Adolescents

The effectiveness of Focalin XR was established in a randomized, double-blind, placebo-controlled, parallel-group study in 103 pediatric patients (ages 6 to 12, n=86; ages 13 to 17, n=17) who met DSM-IV criteria for ADHD. Patients were randomized to receive either a flexible dose of Focalin XR (5 to 30 mg/day) or placebo once daily for 7 weeks. During the first 5 weeks of treatment patients were titrated to their optimal dose and in the last 2 weeks of the study patients remained on their optimal dose without dose changes or interruption.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for Focalin XR– and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the DSM-IV total subscale score of the Conners ADHD/DSM-IV Scales for teachers (CADS-T).

There was a statistically significant treatment effect in favor of Focalin XR. There were insufficient adolescents enrolled in this study to assess the efficacy for Focalin XR in the adolescent population. However, pharmacokinetic considerations and evidence of effectiveness of immediate-release Focalin in adolescents support the effectiveness of Focalin XR in this population.

In two additional studies in pediatric patients ages 6-12 who received 20 mg Focalin XR or placebo in a cross-over design, Focalin XR was found to have a statistically significant treatment effect versus placebo on the Swanson, Kotkin, Agler, M-Flynn & Pelham (SKAMP) rating scale combined score at all time points after dosing in each study (1, 2, 4, 6, 8, 9, 10, 11 and 12 hours in one study and 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours in the other study.)

Adults

The effectiveness of Focalin XR was established in a randomized, double-blind, placebo-controlled, parallel-group study in 221 adult patients (ages 18 to 60) who met DSM-IV criteria for ADHD. Patients were randomized to receive either a fixed dose of Focalin XR (20, 30, or 40 mg/day) or placebo once daily for 5 weeks. Patients randomized to Focalin XR were initiated on a 10 mg/day starting dose and titrated in increments of 10 mg/week to the randomly assigned fixed dose. Patients were maintained on their fixed dose (20, 30 or 40 mg/day) for a minimum of 2 weeks.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for Focalin XR– and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the investigator-administered DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS).

All three Focalin XR doses were statistically significantly superior to placebo. There was no obvious increase in effectiveness with increasing dose.

INDICATIONS AND USAGE

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

The effectiveness of Focalin XR in the treatment of ADHD in patients aged 6 years and older was established in two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD (see CLINICAL STUDIES).

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

Focalin 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 Focalin XR for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Focalin XR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

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

Glaucoma

Focalin XR is contraindicated in patients with glaucoma.

Tics

Focalin XR 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 XR 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

Serious Cardiovascular Events

Sudden Death and Pre-Existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-Existing Psychosis

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

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In the 7-week double-blind placebo-controlled study of Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules, the mean weight gain was greater for patients receiving placebo (+0.4 kg) than for patients receiving Focalin XR (-0.5 kg). Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are

not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Use in Children Under Six Years of Age

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

Drug Dependence

Focalin XR 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

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with dexmethylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for Focalin XR. 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.

Drug Interactions

Focalin XR should not be used in patients being treated (currently or within the preceding two weeks) with MAO Inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Because of possible effects on blood pressure, Focalin XR should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Dexmethylphenidate is metabolized primarily to *d*-ritalinic acid by de-esterification and not through oxidative pathways.

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

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). 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 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 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.

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 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 XR 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 XR is administered to a nursing woman.

Pediatric Use

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

In a study conducted in young rats, racemic 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] of racemic methylphenidate 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 racemic MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules was administered to 46 children and 7 adolescents with ADHD for up to 7 weeks and 206 adults with ADHD in clinical studies. During the clinical studies, 101 adult patients were treated for at least 6 months.

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, MedDRA 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 Acute Clinical Studies with Focalin® XR – Children

Adverse Events Associated with Discontinuation of Treatment

Overall, 50 of 684 children treated with Focalin immediate-release formulation (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). None of the 53 Focalin XR-treated pediatric patients discontinued treatment due to adverse events in the 7-week placebo-controlled study.

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

Table 1 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible Focalin XR doses of 5-30 mg/day. The table includes only those events that occurred in 5% or more of patients treated with Focalin XR and for which the incidence in patients treated with Focalin XR 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–Pediatric Patients

	Focalin®™ XR N=53	Placebo N=47
No. of Patients with AEs		
Total	76%	57%
Primary System Organ Class/ Adverse Event Preferred Term		
Gastrointestinal Disorders	38%	19%
Dyspepsia	8%	4%

Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

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

Adverse Events in Clinical Studies with Focalin® XR – Adults

Adverse Events Associated with Discontinuation of Treatment

In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

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

Table 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. 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. Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment–Adults

	Focalin® XR 20 mg N=57	Focalin® XR 30 mg N=54	Focalin® XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				

Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1] Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

Table 3. Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	Focalin® XR 20 mg (N=57)	Focalin® XR 30 mg (N=54)	Focalin® XR 40 mg (N=54)	Placebo (N=53)
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

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, aggressive behavior

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

Controlled Substance Class

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules, 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.

Poison Control Center

The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

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 dexmethylphenidate from Focalin® XR (dexmethylphenidate 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 for Focalin overdosage has not been established.

DOSAGE AND ADMINISTRATION

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is for oral administration once daily in the morning.

Focalin XR 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). Focalin XR 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 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.

Patients New to Methylphenidate

The recommended starting dose of Focalin XR for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day for pediatric patients and 10 mg/day for adult patients.

Dosage may be adjusted in 5 mg increments to a maximum of 20 mg/day for pediatric patients and in 10 mg increments to a maximum of 20 mg/day for adult patients. In general, dosage adjustments may proceed at approximately weekly intervals. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered.

Patients Currently Using Methylphenidate

For patients currently using methylphenidate, the recommended starting dose of Focalin XR is half the total daily dose of racemic methylphenidate. Patients currently using Focalin (dexmethylphenidate) may be switched to the same daily dose of Focalin XR. The maximum recommended dose is 20 mg/day for pediatric and adult patients.

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 XR. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the

physician who elects to use Focalin XR for extended periods in patients with ADHD should periodically reevaluate 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

Focalin XR capsules 5 mg: light blue (imprinted NVR D5)

Bottles of 100……NDC 0078-0430-05

Focalin XR capsules 10 mg: light caramel (imprinted NVR D10)

Bottles of 100……NDC 0078-0431-05

Focalin XR capsules 15 mg: green (imprinted NVR D15)

Bottles of 100……NDC 0078-0493-05

Focalin XR capsules 20 mg: white (imprinted NVR D20)

Bottles of 100……NDC 0078-0432-05

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

Dispense in tight container (USP).

Focalin® XR is a trademark of Novartis AG

SODAS® is a trademark of Elan Corporation, plc.

This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

REFERENCE

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

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MEDICATION GUIDE

FOCALIN XR®

(dexmethylphenidate hydrochloride) extended-release capsules CII

Read the Medication Guide that comes with FOCALIN XR® before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with FOCALIN XR®.

What is the most important information I should know about FOCALIN XR®?

The following have been reported with use of dexmethylphenidate hydrochloride and other stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting FOCALIN XR®.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with FOCALIN XR®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking FOCALIN XR®.

2. Mental (Psychiatric) problems:

All Patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers

- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking FOCALIN XR®, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What Is FOCALIN XR®?

FOCALIN XR® is a central nervous system stimulant prescription medicine. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD).** FOCALIN XR® may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

FOCALIN XR® should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

FOCALIN XR® is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep FOCALIN XR® in a safe place to prevent misuse and abuse. Selling or giving away FOCALIN XR® may harm others, and is against the law.

Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take FOCALIN XR®?

FOCALIN XR® should not be taken if you or your child:

- are very anxious, tense, or agitated
- have an eye problem called glaucoma
- have tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard to control repeated movements or sounds.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- are allergic to anything in FOCALIN XR®. See the end of this Medication Guide for a complete list of ingredients.

FOCALIN XR® should not be used in children less than 6 years old because it has not been studied in this age group.

FOCALIN XR® may not be right for you or your child. Before starting FOCALIN XR® tell your or your child's doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- seizures or have had an abnormal brain wave test (EEG)

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breast-feeding.

Can FOCALIN XR® be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. FOCALIN XR® and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking FOCALIN XR®.

Your doctor will decide whether FOCALIN XR® can be taken with other medicines.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- antacids
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking FOCALIN XR® without talking to your doctor first.

How should FOCALIN XR® be taken?

- **Take FOCALIN XR® exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Take FOCALIN XR® once each day in the morning. FOCALIN XR® is an extended-release capsule. It releases medicine into your body throughout the day.
- FOCALIN XR® can be taken with or without food. Taking FOCALIN XR® with food may slow the time it takes for the medicine to start working.
- Swallow FOCALIN XR® capsules whole with water or other liquids. **Do not chew, crush, or divide the capsules or the beads in the capsule.** If you or your child cannot swallow

the capsule, open it and sprinkle the small beads of medicine over a spoonful of applesauce and swallow it right away without chewing.

- From time to time, your doctor may stop FOCALIN XR® treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking FOCALIN XR®. Children should have their height and weight checked often while taking FOCALIN XR®. FOCALIN XR® treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much FOCALIN XR® or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of FOCALIN XR®?

See **"What is the most important information I should know about FOCALIN XR®?"** for information on reported heart and mental problems.

Other serious side effects include:

- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

Common side effects include:

- headache
- upset stomach
- trouble sleeping
- anxiety
- decreased appetite
- dry mouth
- dizziness
- nervousness

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

How should I store FOCALIN XR®?

- Store FOCALIN XR® in a safe place at room temperature, 59 to 86° F (15 to 30° C).
- **Keep FOCALIN XR® and all medicines out of the reach of children.**

General information about FOCALIN XR®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOCALIN XR® for a condition for which it was not prescribed. Do not give FOCALIN XR® to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about FOCALIN XR®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOCALIN XR® that was written for healthcare professionals. For more information about FOCALIN XR® call 1-888-669-6682.

What are the ingredients in FOCALIN XR®?

Active Ingredient: dexmethylphenidate hydrochloride

Inactive Ingredients: ammonio methacrylate copolymer, FD&C Blue #2 (5 mg and 15mg strengths), FDA/E172 yellow iron oxide (10 mg and 15mg strengths), gelatin, ink Tan SW-8010, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide, and triethyl citrate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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NOVARTIS

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