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Approved Labeling Attachment

Focalin™ XR

(dexmethylphenidate
hydrochloride)
extended-release capsules



Rx only

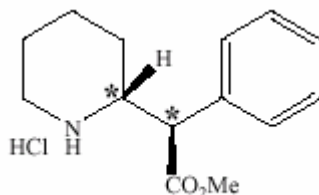
Prescribing Information

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 5, 10, and 20 mg capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, or 10 mg of Focalin™ tablets given b.i.d.

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 $C_{14}H_{19}NO_2 \cdot HCl$. 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 XR also contains the following inert ingredients: ammonio methacrylate copolymer, FD&C Blue #2 (5mg strength), FDA/E172 Yellow Iron Oxide (10mg strength), 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, 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

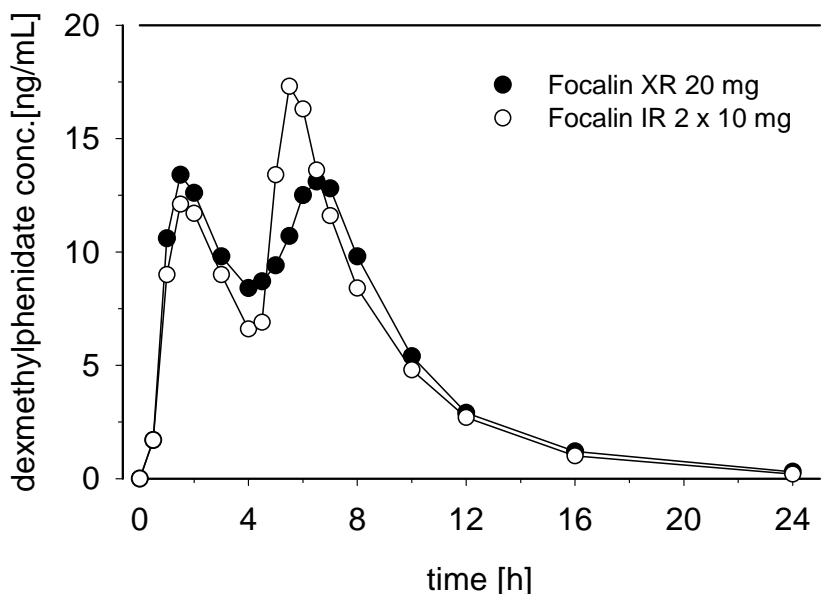
Focalin XR produces a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately four hours apart) when orally administered to healthy adults. The initial rate of absorption for Focalin XR is similar to that of Focalin tablets as shown by the similar rate parameters between the two formulations, i.e., first peak concentration (C_{max1}), and time to the first peak (t_{max1}), which is reached in 1½ 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 is 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 dexamethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12-15 %, independent of concentration. Dexamethylphenidate shows a volume of distribution of 2.65 ± 1.11 L/kg. Plasma dexamethylphenidate concentrations decline monophasically following oral administration of Focalin XR.

Metabolism and Excretion

In humans, dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate did not inhibit cytochrome P450 isoenzymes at concentrations observed after therapeutic doses.

Intravenous dexamethylphenidate 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 dexamethylphenidate 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 inter-peak 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 dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate 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. (For Drug Interactions, see PRECAUTIONS.)

CLINICAL STUDIES

The effectiveness of Focalin XR 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 13-17 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 seven 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.

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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 five 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 two 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 is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged six 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 re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE and ADMINISTRATION).

CONTRAINDICATIONS

Agitation

FocalinTM XR (dexamethylphenidate 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

Depression

FocalinTM XR (dexamethylphenidate hydrochloride) extended-release capsules should not be used to treat severe depression.

Fatigue

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

Long-Term Suppression of Growth

Sufficient data on the long-term effects on growth of dexamethylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted. In the 7-week double-blind placebo-controlled study of Focalin XR, the mean weight gain was greater for patients receiving placebo (+0.4 kg) than for patients receiving Focalin XR (-0.5 kg).

Psychosis

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

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, Focalin XR should be discontinued.

Sudden Death and Pre-Existing Structural Cardiac Abnormalities

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

Hypertension and other Cardiovascular Conditions

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking Focalin XR, especially patients with hypertension. Studies of Focalin XR and methylphenidate have shown small, mean, dose related, increases of resting pulse and blood pressure in both pediatric patients and adults.

Visual Disturbance

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

Use in Children Under Six Years of Age

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

Drug Dependence

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

Patient information is provided at the end of this insert. To assure safe and effective use of Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, the patient information should be discussed with patients.

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 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, dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate 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/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the racemic MRHD on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

Focalin XR 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 Events¹ 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 Events¹ 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, 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 overdose, 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 overdose with methylphenidate.

Recommended Treatment

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

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexamethylphenidate from Focalin™ XR 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 overdose has not been established.

DOSAGE AND ADMINISTRATION

Focalin™ XR 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 dexamethylphenidate 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 (dexamethylphenidate) 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 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

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 20 mg: white (imprinted NVR D20)
Bottles of 100.....NDC 0078-0432-05

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

Dispense in tight container (USP).

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.

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REFERENCE

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

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

Once Daily

Focalin™ XR

(dexamethylphenidate
hydrochloride)
extended-release capsules



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

What is Focalin XR?

Focalin XR is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. Focalin XR contains the drug dexamethylphenidate (Focalin™), a central nervous system stimulant. Dexamethylphenidate Hydrochloride is also found in methylphenidate which has been used to treat ADHD for more than 30 years. Focalin XR is available as 5, 10, and 20 mg extended-release capsules. Focalin XR is taken by mouth, once each day in the morning, before breakfast.

What is Attention Deficit Hyperactivity Disorder?

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

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

How does FOCALIN XR work?

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

Before FOCALIN XR Treatment

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

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

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

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

Who should NOT take FOCALIN XR?

You should NOT take FOCALIN XR if:

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

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

How should I take FOCALIN XR?

Take FOCALIN XR once each day in the morning.

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

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

To sprinkle the contents of the capsule, open the capsule carefully and sprinkle the beads over a spoonful of applesauce. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

If you also take antacids or drugs that suppress stomach acids, you should discuss with your physician or pharmacist how to take these drugs with Focalin XR.

What are the possible side effects of Focalin XR?

The most common side effects of Focalin XR in clinical trials in children over six years old were upset stomach, nausea, decreased appetite, headache and anxiety.

The most common side effects in clinical study of adults were dry mouth, dyspepsia, feeling jittery, dizziness, anxiety and throat pain.

Other side effects seen with dexamethylphenidate include vomiting, dizziness, sleeplessness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

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

Dependence

Abuse of dexamethylphenidate can lead to dependence. Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Blurred Vision

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

Slower Growth

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

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

What must I discuss with my doctor before taking FOCALIN XR?

Talk to your doctor *before* taking FOCALIN XR if you:

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

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

Can I take FOCALIN XR with other medicines?

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

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

Monoamine Oxidase (MAO) Inhibitors

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

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Starting a New Medicine

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

Other Medicines You May Be Taking

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

Other Important Safety Information

Pregnancy and Nursing

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

Overdose

Call a Poison Control Center or your doctor *immediately* if you take more than the amount of Focalin XR prescribed by your doctor.

What else should I know about Focalin XR?

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

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

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

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

Keep out of the reach of children.

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

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

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Gainesville, GA 30504

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