

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FOCALIN safely and effectively. See full prescribing information for FOCALIN.

FOCALIN® (dexamethylphenidate hydrochloride) tablets, for oral use, CII
Initial U.S. Approval: 2001

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- CNS stimulants, including Focalin, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3).
- Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2).

RECENT MAJOR CHANGES

Boxed Warning	1/2019
Contraindications (4)	1/2019
Warnings and Precautions (5)	1/2019

INDICATIONS AND USAGE

Focalin is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (1).

DOSAGE AND ADMINISTRATION

- Administer orally twice daily, 4 hours apart with or without food (2)
- For patients new to methylphenidate: Recommend starting dose of 5 mg once daily (2.5 mg twice daily) (2.2)
- For patients currently taking methylphenidate: Initiate Focalin therapy with half (1/2) the current total daily dose of methylphenidate (2.3)
- Titrate weekly in increments of 2.5 to 5 mg to a maximum of 20 mg/day (10 mg twice daily) (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 2.5 mg, 5 mg, and 10 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or other components of Focalin (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4)

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Events*: Sudden death has been reported in association with CNS-stimulant treatment at usual doses in pediatric

patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, arrhythmias, or coronary artery disease (5.2).

- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risk in patients for whom an increase in blood pressure or heart rate would be problematic (5.3).
- *Psychotic Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for pre-existing psychotic or bipolar disorder prior to Focalin use (5.4).
- *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed (5.5).
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants (5.6).
- *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in the pediatric population (5.7).

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 5% and twice the rate of placebo) in pediatric patients 6 to 17 years were abdominal pain, fever, nausea, and anorexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed (7.1).
- Halogenated Anesthetics: Avoid use of Focalin on the day of surgery if halogenated anesthetics will be used (7.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2019

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Focalin, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see *Warning and Precautions (5.1)*, *Drug Abuse and Dependence (9.2, 9.3)*].

1 INDICATIONS AND USAGE

Focalin is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating pediatric patients and adults with central nervous system (CNS) stimulants, including Focalin, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) [see *Warnings and Precautions 5.2*].

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically reevaluate the need for Focalin use [see *Boxed Warning, Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9)*].

2.2 Pediatric Patients with ADHD

Patients New to Methylphenidate

The recommended starting dose of Focalin for pediatric patients who are not currently taking racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg daily (2.5 mg twice daily) with or without food.

Patients Currently on Methylphenidate

The recommended starting dose of Focalin for pediatric patients currently using methylphenidate is half the total daily dose of racemic methylphenidate.

Titration Schedule

The dose may be titrated weekly in increments of 2.5 to 5 mg to a maximum of 20 mg daily (10 mg twice daily). The dose should be individualized according to the needs and response of the patient.

Maintenance/Extended Treatment

Pharmacological treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of Focalin and adjust dosage as needed.

2.3 Administration Instructions

Focalin is administered orally twice daily, at least 4 hours apart.

2.4 Dose Reduction and Discontinuation

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

3 DOSAGE FORMS AND STRENGTHS

Focalin (dextmethylphenidate hydrochloride) tablets are D-shaped, embossed “D” on upper convex face and dosage strength on lower convex face in the following colors:

- 2.5 mg tablets – blue
- 5 mg tablets – yellow
- 10 mg tablets – white

4 CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or other components of Focalin. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate [*see Adverse Reactions (6.1)*].
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MOAI, because of the risk of hypertensive crises [*see Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including Focalin, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)*].

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Focalin treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Focalin. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including Focalin, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon,

were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in patients 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 patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (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.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Focalin, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Abuse and Dependence [*see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)*]
- Known hypersensitivity to methylphenidate or other ingredients of Focalin [*see Contraindications (4)*]
- Hypertensive crisis with Concomitant Use of Monoamine Oxidase Inhibitors [*see Contraindications (4), Drug Interactions (7.1)*]
- Serious Cardiovascular Reactions [*see Warnings and Precautions (5.2)*]
- Blood Pressure and Heart Rate Increases [*see Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [*see Warnings and Precautions (5.4)*]
- Priapism [*see Warnings and Precautions (5.5)*]
- Peripheral Vasculopathy, including Raynaud's phenomenon [*see Warnings and Precautions (5.6)*]
- Long-term Suppression of Growth [*see Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Focalin in Pediatric Patients with ADHD

The safety data in this section is based on data related to Focalin exposure during the premarketing development program 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 2 controlled clinical studies, 2 clinical pharmacology studies, and 2 open-label long-term safety studies.

Most Common Adverse Reactions (incidence of greater than or equal to 5% and at least twice placebo): abdominal pain, fever, anorexia, and nausea

Adverse Reactions Leading to Discontinuation: Overall, 50 of 684 (7.3%) pediatric patients treated with Focalin experienced an adverse reaction 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).

Table 1 enumerates adverse reactions for two, placebo-controlled, parallel group studies in pediatric patients with ADHD taking Focalin doses of 5, 10, and 20 mg/day. The table includes only those reactions that occurred in patients treated with Focalin for which the incidence was at least 5% and twice the incidence among placebo-treated patients.

Table 1: Common Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class	Adverse Reactions	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%

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of dexamethylphenidate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal: rhabdomyolysis

Immune System Disorders: hypersensitivity reactions such as angioedema, anaphylactic reactions

Adverse Reactions Reported with all Ritalin and Focalin Formulations

The following adverse reactions associated with the use of all Ritalin and Focalin formulations were identified in clinical trials, spontaneous reports, and literature. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Infections and Infestations: nasopharyngitis

Blood and the Lymphatic System Disorders: leukopenia, thrombocytopenia, anemia

Immune System Disorders: hypersensitivity reactions, including angioedema and anaphylaxis

Metabolism and Nutrition Disorders: decreased appetite, reduced weight gain, and suppression of growth during prolonged use in pediatric patients

Psychiatric Disorders: insomnia, anxiety, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), depressed mood

Nervous System Disorders: headache, dizziness, tremor, dyskinesia including choreoathetoid movements, drowsiness, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents) , serotonin syndrome in combination with serotonergic drugs

Eye Disorders: blurred vision, difficulties in visual accommodation

Cardiac Disorders: tachycardia, palpitations, increased blood pressure, arrhythmias, angina pectoris

Respiratory, Thoracic and Mediastinal Disorders: cough

Gastrointestinal Disorders: dry mouth, nausea, vomiting, abdominal pain, dyspepsia

Hepatobiliary Disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus, urticaria, exfoliative dermatitis, scalp hair loss, erythema multiforme rash, thrombocytopenic purpura

Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle cramps, rhabdomyolysis

Investigations: weight loss (adult ADHD patients)

Additional Adverse Reactions Reported with Other Methylphenidate-Containing Products

The list below shows adverse reactions not listed with Ritalin and Focalin formulations [see *Adverse Reactions (6.2)*] that have been reported with other methylphenidate products based on clinical trials data and post-marketing spontaneous reports.

Blood and Lymphatic Disorders: pancytopenia

Immune System Disorders: hypersensitivity reactions such as auricular swelling

Psychiatric Disorders: affect lability, mania, disorientation, libido changes

Nervous System Disorders: migraine

Eye Disorders: diplopia, mydriasis

Cardiac Disorders: sudden cardiac death, myocardial infarction, bradycardia, extrasystole, supraventricular tachycardia, ventricular extrasystole

Vascular Disorders: peripheral coldness, Raynaud's phenomenon

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain, dyspnea

Gastrointestinal Disorders: diarrhea, constipation

Skin and Subcutaneous Tissue Disorders: angioneurotic edema, erythema, fixed drug eruption

Musculoskeletal, Connective Tissue and Bone Disorders: myalgia, muscle twitching

Renal and Urinary Disorders: hematuria

Reproductive System and Breast Disorders: gynecomastia

General disorders: fatigue

Urogenital disorders: priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with Focalin

Table 2 presents clinically important drug interactions with Focalin.

Table 2: Clinically Important Drug Interactions with Focalin

Monoamine Oxidase Inhibitors (MAOI)	
<i>Clinical Impact</i>	Concomitant use of MAOIs and CNS stimulants, including Focalin, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [see <i>Contraindications (4)</i>].
<i>Intervention</i>	Concomitant use of Focalin with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment is contraindicated.
<i>Examples</i>	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
<i>Clinical Impact</i>	Focalin may decrease the effectiveness of drugs used to treat hypertension [see <i>Warnings and Precautions (5.3)</i>].
<i>Intervention</i>	Adjust the dosage of the antihypertensive drug as needed.
<i>Examples</i>	Potassium-sparing and thiazide diuretics, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, centrally acting alpha-2 receptor agonists

Halogenated Anesthetics	
<i>Clinical Impact</i>	Concomitant use of halogenated anesthetics and Focalin may increase the risk of sudden blood pressure and heart rate increase during surgery.
<i>Intervention</i>	Monitor blood pressure and avoid use of Focalin in patients being treated with anesthetics on the day of surgery.
<i>Examples</i>	halothane, isoflurane, enflurane, desflurane, sevoflurane

8 USE IN SPECIFIC POPULATIONS

8.1 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, post-weaning 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 the maximum recommended human dose (MRHD) 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.

8.3 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 is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Focalin have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials [see *Clinical Studies* (14)].

The safety and effectiveness of Focalin in pediatric patients less than 6 years have not been established.

The long-term efficacy of Focalin in pediatric patients has not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including Focalin. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions* (5.7)].

Juvenile Animal Toxicity Data

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 to 14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the MRHD of 60 mg 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 MRHD of 60 mg of racemic methylphenidate on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD of 60 mg of racemic methylphenidate on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Focalin has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Focalin contains dextmethylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including Focalin, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is characterized by impaired control over drug use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which may result in overdose and death [*see Overdosage (10)*].

To reduce the abuse of CNS stimulants including Focalin, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants [*see How Supplied/Storage and Handling (16)*], monitor for signs of abuse while on therapy, and reevaluate the need for Focalin use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants, including Focalin.

Dependence

Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including Focalin. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

Human Experience

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, and rhabdomyolysis.

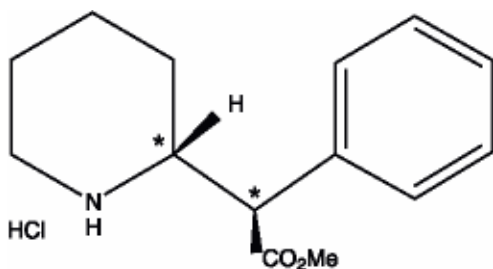
Overdose Management

Consult with a Certified Poison Control Center (1-800-222-1222) for latest recommendations.

11 DESCRIPTION

Focalin contains dextmethylphenidate hydrochloride, a CNS stimulant. Dextmethylphenidate hydrochloride is the *d-threo* enantiomer of racemic methylphenidate hydrochloride. Focalin is available as 2.5 mg, 5 mg, and 10 mg strength tablets for oral administration.

Chemically, dextmethylphenidate hydrochloride is methyl α -phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its molecular formula is C₁₄H₁₉NO₂•HCl. 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. Its molecular weight is 269.77 g/mol.

Inactive ingredients: FD&C Blue No.1 #5516 aluminum lake (2.5 mg tablets), FD&C Yellow Lake #10 (5 mg tablets). The 10 mg tablets contain no dye. Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmethylphenidate hydrochloride is a CNS stimulant. The exact mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Pharmacodynamics

Dexmethylphenidate is the more pharmacologically active *d*-enantiomer of racemic methylphenidate. 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.

Cardiac Electrophysiology

A formal QT study has not been conducted in patients taking Focalin; however, a large QT effect is not expected. At the recommended maximum total daily dosage of 40 mg, Focalin XR (dexmethylphenidate) extended-release capsule does not prolong the QTc interval to any clinically relevant extent.

12.3 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 1.5 hours postdose. 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.

After single dose administration of Focalin to pediatric patients, dexmethylphenidate exposure (C_{max} and AUC_{0-inf}) showed dose-proportional increase in the range of 2.5 mg to 10 mg. Comparable plasma dexmethylphenidate levels were achieved following single *dl-threo*-methylphenidate HCl doses given as capsules in twice the total mg amount (equimolar with respect to Focalin).

Approximately 90% of the dose is absorbed after oral administration of radiolabeled racemic methylphenidate. However, due to first pass metabolism the mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22% to 25%.

Effect of Food

High fat breakfast did not significantly affect C_{max} or AUC_{0-inf} of dexmethylphenidate when two 10 mg Focalin tablets were administered, but delayed T_{max} from 1.5 hours post dose to 2.9 hours post dose.

Distribution

The plasma protein binding of dexmethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12% to 15%, independent of concentration. Dexmethylphenidate shows a volume of distribution of 2.65 ± 1.11 L/kg.

Elimination

Plasma dexamethylphenidate concentrations declined exponentially following oral administration of Focalin. Intravenous dexamethylphenidate was eliminated with a mean clearance of 0.40 ± 0.12 L/hr/kg. The mean terminal elimination half-life of dexamethylphenidate was approximately 2.2 hours.

Metabolism

In humans, dexamethylphenidate is metabolized primarily via de-esterification to d- α -phenyl-piperidine acetic acid (also known as *d*-ritalinic acid). This metabolite has little or no pharmacological activity. There is little or no *in vivo* interconversion to the *l*-threo-enantiomer.

Excretion

After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic *dl*-methylphenidate was *dl*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5% of an intravenous dose.

Studies in Special Populations

Male and Female Patients

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

In a single dose study conducted in adults, the mean dexamethylphenidate AUC_{0-inf} values (adjusted for body weight) following single two 10 mg doses of Focalin were 25% to 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.

Racial or Ethnic Groups

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

Pediatric Patients

The pharmacokinetics of dexamethylphenidate 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 dexamethylphenidate was similar, however, pediatric patients showed somewhat lower AUCs compared to the adults.

Patients with Renal Impairment

There is no experience with the use of Focalin in patients with renal impairment. Since renal clearance is not an important route of methylphenidate clearance, renal impairment is expected to have little effect on the pharmacokinetics of Focalin.

Patients with Hepatic Impairment

There is no experience with the use of Focalin in patients with hepatic impairment.

Drug Interaction Studies

Methylphenidate is not metabolized by cytochrome P450 (CYP) isoenzymes to a clinically relevant extent. Inducers or inhibitors of CYPs are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the *d*- and *l*-enantiomers of methylphenidate did not relevantly inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A. Clinically, methylphenidate coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies have not been carried out with dexamethylphenidate. 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 was seen at a daily dose of approximately 60 mg/kg/day. This dose is approximately 2 times the MRHD of 60 mg of racemic methylphenidate in pediatric patients on a mg/m² basis. 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, which is approximately 4 times the MRHD of 60 mg of racemic methylphenidate in pediatric patients on a mg/m² basis.

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

Mutagenesis

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

Impairment of Fertility

No human data on the effect of methylphenidate on fertility are available.

Fertility studies have not been conducted with dexmethylphenidate. 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, approximately 10-fold the maximum recommended dose of 60 mg of racemic methylphenidate in adolescents on a mg/m² basis.

14 CLINICAL STUDIES

The efficacy of Focalin for the treatment of ADHD was established in two double-blind, parallel-group, placebo-controlled trials in untreated or previously treated patients (ages 6 to 17 years old) who met DSM-IV criteria for ADHD inattentive, hyperactive-impulsive, or combined inattentive/hyperactive-impulsive subtypes. The sample was predominantly younger (ages 6 to 12 years); thus, the findings are most pertinent to this age group.

In Study 1, patients were randomized to receive either Focalin (5, 10, or 20 mg/day total dose), racemic methylphenidate HCl (10, 20, or 40 mg/day total dose), or placebo in a multicenter, 4-week, parallel group study in 132 pediatric patients. Patients received study medication twice daily separated by a 3.5 to 5.5 hours interval. 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 primary outcome was change from baseline to week 4 of the average score (an average of 2 ratings during the week) of the teacher's version of the SNAP-ADHD Rating Scale. This 18 item scale measures ADHD symptoms of inattention and hyperactivity/impulsivity, rated on a scale of 0 (Not at All) to 3 (Very Much). Patients treated with Focalin showed a statistically significant improvement in symptom scores from baseline over patients who received placebo (Table 3).

Table 3: Summary of Efficacy Results from ADHD Acute-Phase Study in Pediatric Patients (6 – 17 years) (Study 1)

Study Number	Treatment Group	Primary Efficacy Measure: Teacher SNAP-ADHD Total Score ^a	
		Mean Baseline Score (SD)	Mean Change from Baseline Week 4 Score (SD)
Study 1	Focalin 5-20 mg/day ^b (n = 44)	1.4 (0.7) (n = 42)	- 0.7 (0.7) (n = 42)
	Placebo (n = 42)	1.6 (0.7) (n = 41)	- 0.2 (0.7) (n = 39)

Abbreviations: SD: standard deviation; n = number of patients available at the assessment time point.

^aAverage of two ratings.

^bStatistically significantly different from placebo.

Study 2 was a multicenter, placebo-controlled, double-blind, 2-week treatment withdrawal study in 75 children (ages 6 to 12 years) 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 (Table 4).

Table 4: Summary of Efficacy Results from ADHD Randomized Withdrawal Study in Pediatric Patients (6 – 17 years) (Study 2)

Study Number	Treatment Group	Primary Efficacy Measure: Proportion of Treatment Failure ^a	
		Number of Treatment Failures /Number of Randomized Patients	Percentage
Study 2	Focalin 5-20 mg/day ^b	6/35	17.1%
	Placebo	25/40	62.5%
^a One patient did not have the value at Visit 10 and hence not included in this analysis.			
^b Statistically significantly different from placebo.			

16 HOW SUPPLIED/STORAGE AND HANDLING

Focalin (dextmethylphenidate hydrochloride) tablets (D-shaped, embossed “D” on upper convex face and dosage strength on lower convex face) are available as follows:

- 2.5 mg tablets (NDC 0078-0380-05) blue, supplied in bottles of 100
- 5 mg tablets (NDC 0078-0381-05) yellow, supplied in bottles of 100
- 10 mg tablets (NDC 0078-0382-05) white, supplied in bottles of 100

Store at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Dispense in tight, light-resistant container (USP).

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired Focalin by a medicine takeback program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix Focalin with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard Focalin in the household trash.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients that Focalin is a controlled substance, and it can be abused and lead to dependence. Instruct patients that they should not give Focalin to anyone else. Advise patients to store Focalin in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired Focalin by a medicine take-back program if available [see *Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2, 9.3), How Supplied/Storage and Handling (16)*].

Serious Cardiovascular Risks

Advise patients that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with Focalin use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [see *Warnings and Precautions (5.2)*].

Blood Pressure and Heart Rate Increases

Instruct patients that Focalin can cause elevations of their blood pressure and pulse rate [see *Warnings and Precautions (5.3)*].

Psychiatric Risks

Advise patients that Focalin, at recommended doses, can cause psychotic or manic symptoms, even in patients without prior history of psychotic symptoms or mania [see *Warnings and Precautions (5.4)*].

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct them to seek immediate medical attention in the event of priapism [*see Warnings and Precautions (5.5)*].

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

Instruct patients beginning treatment with Focalin about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking Focalin. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [*see Warnings and Precautions (5.6)*].

Suppression of Growth

Advise patients that Focalin may cause slowing of growth and weight loss [*see Warnings and Precautions (5.7)*].

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East Hanover, New Jersey 07936

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MEDICATION GUIDE
FOCALIN® (foh-kuh-lin)
(dexamethylphenidate hydrochloride)
tablets CII

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

FOCALIN is a federal 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 abused or been dependent on alcohol, prescription medicines, or street drugs.

The following have been reported with use of methylphenidate 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 you 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**
- **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 (CNS) prescription medicine. **It is used for the treatment of Attention-Deficit 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.

Who should not take FOCALIN:

FOCALIN should not be taken if you or your child:

- are allergic to methylphenidate hydrochloride, or any of the ingredients in FOCALIN. See the end of this Medication Guide for a complete list of ingredients in FOCALIN.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.

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
- circulation problems in fingers or toes
- if you are pregnant or plan to become pregnant. It is not known if FOCALIN will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.

- if you are breastfeeding or plan to breastfeed. FOCALIN passes into your breast milk. You and your doctor should decide if you will take FOCALIN or breastfeed.

Tell your doctor about all of the medicines that you or your child takes including prescription and over-the-counter 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
- blood pressure medicines (anti-hypertensive)

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

- You should not take FOCALIN on the day of your operation if a certain type of anesthetic is used. This is because there is a chance of a sudden rise in blood pressure and heart rate during the operation.

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 daily, at least 4 hours apart.
- FOCALIN may 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.
- **In case of poisoning call your poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.**

What are the possible side effects of FOCALIN?

FOCALIN may cause serious side effects, including:

- See “**What is the most important information I should know about FOCALIN?**” for information on reported heart and mental problems.
- **painful and prolonged erections (priapism)** have occurred with methylphenidate. If you or your child develops priapism, seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- **circulation problems in fingers and toes** (Peripheral Vasculopathy, including Raynaud’s phenomenon):
 - fingers or toes may feel numb, cool, painful
 - fingers or toes may change color from pale, to blue, to red

Tell your doctor if you or your child have, numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.

- **Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking FOCALIN.**
- **slowing of growth (height and weight) in children**

Common side effects include:

- abdominal pain
- fever
- anorexia
- nausea

Call your doctor for medical advice about side effects. **You may report side effects to FDA at 1-800-FDA-1088.**

How should I store FOCALIN?

- Store FOCALIN in a safe place and in a tightly closed container at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect from light.
- Dispose of remaining, unused, or expired FOCALIN by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix FOCALIN with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away (discard) FOCALIN in the household trash.
- **Keep FOCALIN and all medicines out of the reach of children.**

General information about the safe and effective use of FOCALIN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about FOCALIN that is written for healthcare professionals. 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 symptoms that you have. It may harm them and it is against the law.

What are the ingredients in FOCALIN?

Active ingredient: dexamethylphenidate 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.

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For more information, call 1-888-669-6682.

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

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